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VISUAL DISTURBANCES PRODUCED BY BILATERAL LESIONS OF THE OCCIPITAL LOBES WITH CENTRAL SCOTOMAS

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Experience in the last war has shown that injuries to both occipital lobes result in total blindness. The blindness, however, is rarely permanent.[1] As a rule, there is progressive restitution of vision although recovery is seldom complete. In many cases careful perimetric examination may reveal residual scotomas in the homonymous fields of vision. The degree of partial blindness depends on the extent of the damage to the calcarine cortex. In addition to field defects, certain physiologic and psychologic mechanisms of vision may become apparent in these cases through special examinations. Interesting descriptions of qualitative and quantitative changes in restitution of visual function may also be volunteered by the patient. Recently, we had the opportunity to study several persons with battle wounds of both occipital lobes. One of the patients presented a remarkable clinical picture throughout the period of recovery, and his case is herewith described in detail.[2]

REPORT OF A CASE

History.—A Marine, private first class, aged 23, was struck in the occiput by enemy gunfire. As soon as he was hit, he fell and apparently lost consciousness. He was given emergency treatment, and when he recovered, within several hours, he was totally blind, unable even to see light. Two days later he appreciated light, but everything appeared to him to be a "milky haze or dense fog." He could not recognize any movement until nine days after the injury.

Examination.—Physical examination at an overseas base hospital revealed two almost healed, clean bullet wounds, each located exactly 1 inch (2.54 cm.) superior to and 2 inches (5 cm.) lateral to the right and the left of the inion of the occiput. The hole on the right side was larger than the one on the left, and, according to the records, the direction of enemy firing was from the patient's right side. The right pupil measured 5 mm. and the left pupil 3 mm. Both responded to light, but the left one reacted better than the right. There was no ptosis or palsy of the ocular muscles. A transient nystagmus was noted, especially on lateral gaze to the right. Both optic fundi showed papilledema. Grossly, no definite visual defects could be plotted. Subjectively, the patient felt that he was perceiving with his central fields of vision. The rest of the neurologic examination gave essentially normal results. A roentgenogram of the skull disclosed two irregular defects in the left and right occipital bones respectively, with intercommunicating fracture lines between the two. In addition, bony fragments were noted to extend intracranially for 2 cm. from the occiput (fig. 1*A*). Ventriculographic examination, performed because of papilledema, showed slight upward elevation of the right posterior horn (fig. 1*B*). There was no evidence of subdural or subarachnoid hemorrhage, and on the surface the cortex appeared normal. The patient was treated conservatively and continued to improve.

Progress.—Thirty-five days after the injury the patient was able to appreciate the presence and contrast of objects in his surroundings. He made the interesting observation that his vision seemed to be equally good in the central and in the peripheral part of the field of vision. All objects, however, appeared to him to be obscured by a "dense fog." Special psychologic tests showed no intellectual impairment. Comprehension and reaction times were normal. Physical and neurologic examination showed no deviation from previous records except that the papilledema had receded.

Forty-three days after the injury a craniotomy was performed, and fragments of bone were removed from the left side (fig. 2). The cortex of both occipital poles was observed to be damaged, and the adjacent subcortex on the right side showed a large degenerative cyst. One week later the patient complained of numbness, tingling and inability to recognize objects in the finger tips of either hand. Examination disclosed bilateral impairment of stereognosis, position sense and two point discrimination. These defects were mild and transient. His vision continued to improve.

Two months after the injury rough perimetric examination disclosed large, absolute central scotomas in both eyes, each surrounded by relative scotomatous defects. The latter seemed to be less intense toward the periphery of the field of vision. Unconsciously,

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1. Klüver, H.: Visual Disturbances After Cerebral Lesions, Psychol. Bull. **24**:316-358, 1927. Wilbrand, H., and Saenger, A.: Die Verletzungen der Sehbahn des Gehirns mit besonderer Berücksichtigung der Kriegsverletzungen, Wiesbaden, J. F. Bergmann, 1918.

2. The other patients in this series revealed similar symptoms, but to a lesser degree.

the patient had a great tendency to fix with his peripheral field of vision. He was unaware of the large scotomas in his central fields of vision, and he could not be convinced that he was actually seeing with his peripheral retina. To him objects appeared to be in the middle of his field of vision. One week after this examination the fields were plotted on a tangent screen at a distance of 1 meter, ocular fixation being maintained with his peripheral field of vision. These fields showed scotomas extending 20 degrees from the central point for motion of a 10 mm. test object. There was no color perception. Peripherally, he could detect motion, direction of movement and objects described by motion, such as a drawn circle, a triangle, the number 4 and the letter A. He claimed that whatever vision he had seemed to be clearer with low illumination.

Ten weeks after the injury he began to notice large print. He was still under the impression that he saw with his central field of vision. The image was indistinct, and all he could actually distinguish was contrast between black and white. Color perception had not yet returned. Opticomotor nystagmus could be elicited when he fixed with his peripheral field of vision.

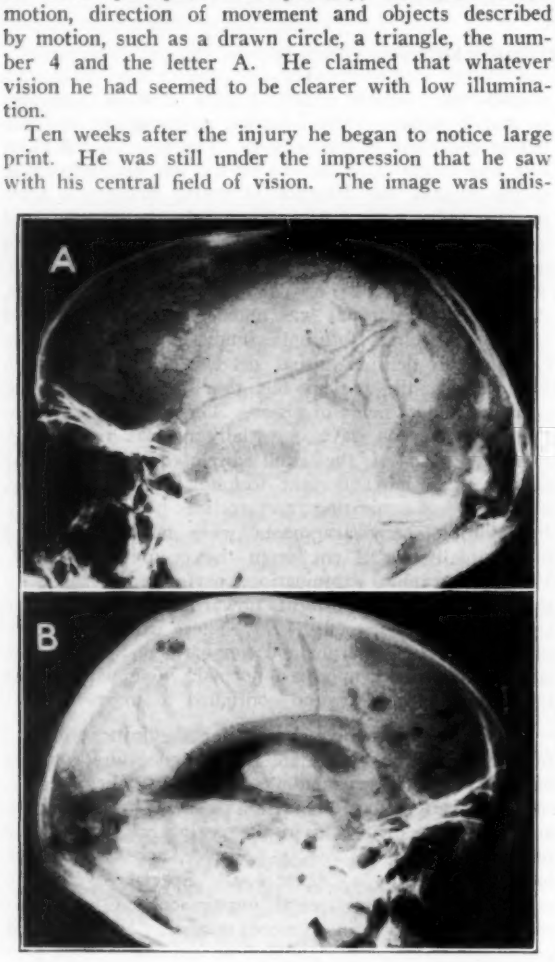

Fig. 1.—*A*, roentgenogram of the left side of the skull, revealing defects and scattered fragments of bone extending intracranially from the occiput. *B*, ventriculogram of the right side, showing elevation of the posterior horn of the right lateral ventricle.

Eleven weeks after the injury the patient volunteered that he saw much better at night or in the dark, when he could recognize objects, and even some color. On cloudy days or at dusk he could count fingers and thought he could identify red and yellow in the peripheral portion of the left field of vision. Dark adaptation time measured on the Feldman adaptometer was nine minutes. Subsequent examinations by other methods also showed prolongation of the dark adaptation time.

Three months after the injury the visual fields were plotted on a tangent screen at a distance of 35 cm. under illumination of 3.5 foot candles. The size of the test object used was 10 mm. The plotted fields revealed large bilateral central scotomas extending 15 degrees from the central point. The absolute scotoma was surrounded by concentric zones of relative loss of vision, the defects being less conspicuous toward the periphery of the field of vision.

Six months after the injury the extent of the central scotoma remained unchanged. In the left upper quadrants of the fields of vision the patient was able to recognize a yellow pencil with a small red top. This image, he claimed, fluctuated in brightness and clearness. Seven months after the injury, in the right upper quadrants he identified the color of small test objects (fig. 3). In other quadrants he recognized form and shape, such as geometric figures or letters of the alphabet.

From this time he was able to walk about without assistance. He was not, however, certain or confident of walking unaided in the street. Further recovery was slow. The visual fields were practically unchanged. Five months after the injury after-imagery could not be induced irrespective of the quantity or quality of the light stimulus applied.[3]

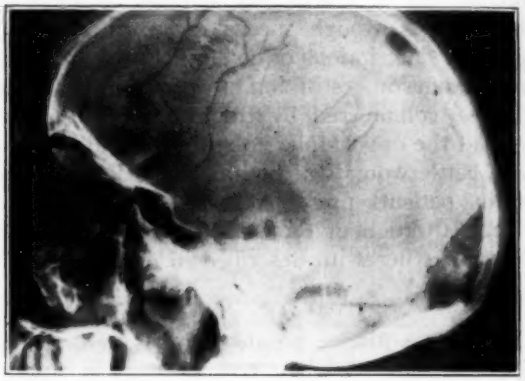

Fig. 2.—Roentgenogram of the left side of the skull after removal of fragments of bone.

COMMENT

In order not to lose the significance of the signs and symptoms noted during the convalescent period, each will be described and discussed under its own heading.

Perception of Light.—The first visual function, which returned two days after the patient was injured, was that of light perception. He stated: "What I saw was a milky fog." Everything before him seemed to be a glare. A bright

3. In the cases of patients with less extensive defects of the central visual field, after-imagery could be elicited, but the responses varied. In a patient with three fourths of his binocular field of vision defective, the shining of a round light into either eye produced an angular or square, gray image, which showed no fluctuation in color except for a transient maroon, a blue tint or a darkening of the tone of gray.

object or sunlight was unpleasant to him. He constantly sought shady areas and avoided sunlight because he felt more comfortable in the dark. For this reason, he independently purchased dark lenses and wore them religiously during the day. He claimed he felt better on cloudy days and at night. Three months after the injury he noted that he perceived movement or outlines of objects best in the dark or at night. He stated: "I can see better in total darkness. At times I could see the outline of a flying airplane at night. When I come out of a dark room into a bright room, my eyes hurt, and it makes me blink." He also found that he recognized an object with a dark background better than when it was silhouetted against a light or a bright field. Under bright illumination he identified the presence of an object better when it was in motion. Obviously, on sunny days his vision was poor.[4] Later in the stage of his recovery, he complained that the glossiness, luminosity or brightness of an object interfered with his visual recognition, or even with his "desire" to perceive the object.

Since central vision was destroyed the patient was day blind. What vision he possessed seemed to function best with low illumination; and since this condition is characteristic of the peripheral part of the retina, it confirms the results of examination of the visual fields, namely, loss of central vision and retention of peripheral vision due to damage to the occipital cortex.

Brightness also interfered with his perception of color and form, and even of motion. Interesting psychologic reactions were the unpleasant emotional experiences he had while exposed to illumination and his relative sense of security and calmness when in the dark.

Perception of Movement.—Almost as soon as the patient was able to distinguish between light and dark he recognized movement of large objects, such as the waving of a hand or an arm in his peripheral fields of vision. Five weeks after the injury the patient noted that he could "guess" at objects in his surroundings, such as pieces of furniture, but only while he was in motion. When he was standing still he did not see much. This is an example of appreciation of relative movement. Everything before him appeared foggy, and he did not even attempt to look at stationary objects. He was under the constant impression that he perceived movement with his central fields of vision. Repeated examination, however, showed that he was totally blind in the central fields of vision and that he appreciated movement keenly in the peripheral fields. In fact, here he was able to perceive form and shape of objects delineated by movements. He recognized only geometric figures, letters or numbers when they were drawn in the peripheral visual fields. Often, he reflexly tilted his head and eyes so as to regard the moving object in question with his paracentral field of vision.

Biologically, appreciation of movement is one of the most primitive forms of visual functions

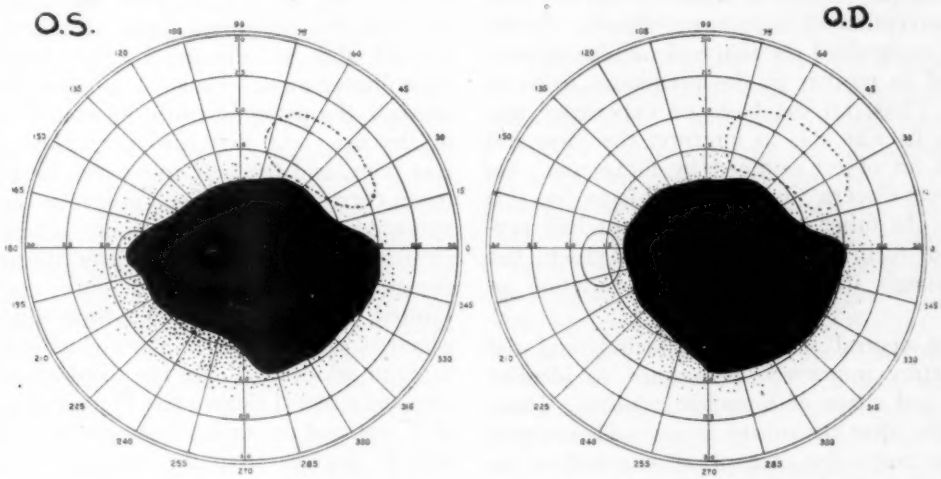

Fig. 3.—Visual fields plotted on a tangent screen six months after injury to both occipital lobes. Size of test object, 10 mm.; distance, 35 cm; illumination, 3.5 foot candles. The solid black area represents absolute scotoma, and the stippled area, relative blindness, which is most pronounced centrally and less evident toward the periphery. The line of dots represents an area in which color vision was preserved. The patient was able to recognize the shape of large objects in the left inferior quadrants and the color of large test objects under low illumination in parts of the upper and lower quadrants of the left fields of vision.

4. This was also true of other patients with battle injuries of both occipital lobes.

and one of the most essential features in the vision of lower animals. It is a function par excellence of the peripheral portion of the retina. Our patient manifested all the physiologic functions of this part of the retina—in his case, the peripheral "cortical retina." He had no central vision. It is apparent from this case that in man, too, appreciation of movement is well developed in the peripheral fields of vision, but his visual perception in general depends largely on recognition of form, a function of central vision.

Perception of Form.—The power of identifying the form or shape of objects is based on visual acuity, experience and interpretation. Since visual acuity is highest in the central field of vision, it is obvious that appreciation of still objects is achieved mostly with the macula and least with the peripheral field of vision. Because our patient had no central vision, he did not have much perception of stationary objects. However, he recognized the shape of familiar objects described in motion in the peripheral fields of vision. Thus, on the basis of experience and memory, he was able to interpret the form and shape of an object outlined by movement. He could not discern unfamiliar objects in this manner. In other words, the patient had perception of form with his peripheral vision, but only through the medium of appreciation of motion.

As the central scotoma contracted, and the visual acuity improved, he learned to identify the size and shape of immobile articles. Thus, six months after the injury he guessed correctly the shape and color of a pencil exposed in his paracentral field of vision. After seven months he perceived, without too much difficulty, the shape of a 2 inch (5 cm.) square or circle and the letter H when presented in the left homonymous fields of vision, about 20 degrees from the fixation point. He failed when presented with unfamiliar drawings, such as Roman numerals or a mirror-imaged *E*.

During the period of recovery he showed an interesting psychologic mechanism. He had a great tendency to fill in defects in his visual perception. Even when he had little vision and images were not clear, it seemed to him that he saw the whole object. Thus, when he was presented with a familiar article, he felt certain that he saw it completely and proceeded to describe its gross shape, and even color. The description was frequently correct; but when he was confronted with an unfamiliar object, he failed in his endeavors. In fact, he did not even attempt to look at the exposed object. Evidently, the apparent appreciation of form was based largely on experience and meaning, and only partly on the acuity which was present in small islands in his peripheral field of vision. Psychologically, he respected the fact that he could not see, and thus he avoided situations which would elicit his failures in vision. He tackled only images which appeared familiar. What the patient's symptoms demonstrated here was the principle of gestaltism, or that of appreciation of the form of an object as a whole by psychologic filling in of the defects of the perceived retinal image.[5]

Perception of Color.—The patient had no color perception until eleven weeks after the injury, when he began to guess at colors of very large objects. Thus, he "thought" he saw a yellow pencil, declaring, "I believe I can see some color. I think I can see the yellow in that pencil." After that incident, he began to search for color by turning his head and eyes so as to fix with his peripheral fields of vision, and he noticed that he discerned color better under poor illumination. Thus, one night when a plane crashed, the patient claimed he saw the red glow of the fire. At first his appreciation of color was poor, and the only one which he seemed to name correctly was red. Otherwise, everything appeared to have a gray tone. However, he improved, and five months after the injury he recognized red, green and blue neon signs. Plotted visual fields at this time disclosed an island of color vision in the right homonymous superior quadrants. He identified correctly red, blue and green 1 degree test objects at a distance of 27 cm. and under 3.5 foot candles of illumination 15 degrees from the macula.

Appreciation of colors is not a uniform function of the retina. When the eye is light adapted, the extreme periphery of the retina is monochromatic, or color blind. This, however, is only relative. If the stimulus is feeble, color sensation is absent in all parts of the retina. If the intensity of the light is increased, the field gradually extends until eventually most colors become apparent at the periphery. In a similar manner, variation of the area or size of the tested color objects influences the extent of the field for color vision. In general, color vision is less sensitive in the peripheral than in the central part of the fields in the light-adapted eye.[6] In our patient, the chromatic response in bright illumination was nil, an observation seemingly contradicting the foregoing statements. However, it must be remembered that our patient was relatively day blind and

5. Goldstein, K.: After-Effects of Brain Injuries in War, New York, Grune & Stratton, Inc., 1942.

6. Duke-Elder, W. S.: Text-Book of Ophthalmology, St. Louis, C. V. Mosby Company, 1938.

that his remaining vision depended on peripheral retinal function. Also, bright illumination or a glare produced a psychologic resistance to visual perception, and thus it could not be determined with certainty whether the patient could or could not appreciate color in the light-adapted eye.

Under conditions of dark adaptation color sensitivity is also greatest in the macular region, but it falls off much more rapidly and is much more restricted toward the periphery. Of all colors, sensitivity to red, however, extends to the extreme periphery.[6] This should explain why our patient saw the red glow of a burning plane at night twelve weeks after the injury. In summary, it appears that the patient's responses to color stimuli were the responses expected of a person with visual function limited to the peripheral field.

Subjective Visual Phenomena.—As previously noted, the patient disliked to look at bright objects or illuminated areas. He claimed it was disagreeable and that it interfered with the little vision he possessed. Three months after the injury, he stated: "When I look straight ahead, I see heat waves rising in front of me. The waves seem to be directly before me. I cannot tell whether or not I see better with the side of my eyes. Sometimes it seems as if the sun were shining on ice, and little spots of moisture were rising." He first noticed the appearance of these waves soon after "foggy vision" began to improve. Subsequent observations by the patient disclosed that he saw these "moving heat waves," or "radiations," every time he gazed at a bright background.[7] The more intense and brighter the sun, the more vivid were the emanating waves before him. The rate of radiation of the "heat waves" seemed to increase with the luminosity of the background. With this increase in radiation there was a decrease in visual perception of objects in his surroundings. The patient stated: "The more sunlight there is, the thicker and denser the waves and the greater the haze before me. Increased light makes the radiations, which seem to go upward in a spiral, move faster. These waves are made up of circles all mixed up and moving in all directions, but they seem to be going chiefly upward."

What this patient described were phenomena of entoptic vision. It is well known that if a brightly illuminated surface, such as the sky or a fluorescent screen, is regarded by the normal subject, a great number of small, bright dancing spots appear on a relatively dark background, shooting upward, darting rapidly along a circuitous path and disappearing as abruptly as they come. According to one theory these images are due to visibility of red blood corpuscles, or the spaces between them, moving through the capillaries.

About five months after the injury, the patient remarked that when he looked at an object directly before him, it tended to wax and wane; he declared: "The object fades quickly and becomes somewhat clearer in a short time. When it fades, it becomes grayer. When it gets clear, it appears darker gray and less foggy." When the patient fixed on an object, such as a large pencil, in ordinary room light, he described periodic variations in the perceptible visual acuity. This fluctuation in visual perception is a normal phenomenon and may be easily demonstrated under certain conditions.[8] It is more evident with threshold stimuli.

Orientation of Field of Vision.—Psychologically, the patient showed an interesting phenomenon, that of persistent displacement of the perceived image from the seeing peripheral to the nonseeing central field of vision. Throughout his period of convalescence the patient felt that he perceived objects in space, although not clearly, just as he always had prior to the injury. He insisted he saw objects directly before him with the central parts of his fields of vision. It was difficult to convince him that his central fields were totally blind. He was unable to detect the blind areas when he viewed articles or people before him, and it seemed that he made no effort to search for the scotomas. Everything before him seemed to be of uniform visual intensity. In gross tests, a large central absolute scotoma could be elicited in each eye. This was demonstrated to the patient on repeated occasions throughout the period of convalescence, but only with great reluctance did he accept the fact that there was no vision in this zone. In spite of this admission, six months after the injury, he still declared, "I cannot see any black spot or blind area before me. I still do not believe I am blind in the center, though you proved it to me. People tell me I move my eyes around when I try to look at things; so I must be using the side of my eyes, but even then it is hard to believe."

This is a type of disturbance in space perception in which the localization of an object is relative; the perception of a point in the subjective visual space is relative to the fixation point. A patient with scotoma has his visual

7. Other men with bilateral lesions of the occipital lobe had similar subjective visual phenomena. One of them had such symptoms even with the eyes closed.

8. Guilford, J. P.: Fluctuations of Attention with Weak Visual Stimuli, Am. J. Psychol. **38**:534-583, 1926.

fields psychologically organized in the same manner as has a normal person. As Klüver put it: "There is a 'right' and 'left' side, and 'above' and 'below' and a special center which is 'straight forward' or 'just before me'" in the remaining field of vision. The special center is in the perceptive zone and determines the subjective median point, whereas the objective median point may lie in the blind field. However, in our patient the subjective median point was projected psychologically into the blind field because there was no zone of remaining vision which had the power to perceive form or to hold his attention. He was unable to establish a pseudofovea, that is, a fovea in the functional sense, until he could appreciate size and shape of objects with a part of the residual field of vision. When such restitution became manifest, seven months after the injury, he formed a new center of distinctness, or a new functional fovea, and he no longer projected his subjective median point into the blind macular area. His psychologic field of vision became reorganized about the new functional macula. Interestingly, when a new functional fovea was formed, he could be convinced that he was using his peripheral vision, and he finally admitted that people "must have been right" when they told him he was moving his "eyes around in looking at things." In other words, not until his psychologic field of vision was reorganized did he relinquish his old pattern of vision.

SUMMARY

1. A patient with bilateral lesions of the occipital lobe showed a series of visual disturbances due to loss of central vision in each eye. After he had been completely amaurotic, vision returned in the peripheral fields, and restitution continued to take place medially, terminating in bilateral large central scotomas. During his period of recovery he had good perception of motion, defective color vision, little appreciation of form and ability to see best in the dark or in low illumination, all visual functions characteristic of the peripheral portions of the retina (in this case the peripheral "cortical retina").

2. The patient also manifested (*a*) the normal mechanism of psychologic filling in of visual field defects, thus perceiving objects as a whole; (*b*) retention of his psychologic field of vision about a subjective central point in a blind area, which made it difficult for him to realize that his central vision was lost; (*c*) reorganization of his psychologic field of vision when a new functional fovea was formed; (*d*) entoptic phenomena, with visualization of emanating "waves" and (*e*) fluctuation of perception in the remaining field of vision.

3. Opticomotor nystagmus was induced by having a striped drum revolve in his peripheral, but not in his central, fields of vision. Five months after the injury after-imagery could not be elicited with a light stimulus placed in any part of the field of vision.

VASOTHROMBOSIS OF THE CENTRAL NERVOUS SYSTEM

A CHARACTERISTIC VASCULAR SYNDROME CAUSED BY A PROLONGED STATE OF VASOPARALYSIS

I. MARK SCHEINKER, M.D.

CINCINNATI

Putnam and his co-workers [1] were the first to call attention to the importance of local circulatory disturbances caused by venous obstruction, and they demonstrated clearly its significance in cases of disseminated sclerosis. Putnam has approached the subject from many different avenues and has established important data extending far beyond the problem of pathogenesis of multiple sclerosis. It is surprising how few histopathologic studies concerning the alterations of the venous circulation in the brain are available. Several aspects of the morphologic characteristics of venous thrombosis and its pathogenesis remain obscure. One needs particularly to know more of the early stage of the pathologic process.

It is the purpose of this presentation to report observations in a series of cases in which thrombosis was confined to the smaller veins and capillaries and to discuss the pathogenesis of the lesions. Special attention will be paid to the earliest manifestation of the pathologic process and to the relation to "vasoparalysis of the central nervous system," a recently described vascular syndrome.[2]

REPORT OF TWO ILLUSTRATIVE CASES

CASE 1.—A Negro woman aged 23 was first admitted to the Cincinnati General Hospital on Sept. 6, 1938, with the following history: She was in excellent health until three days prior to admission when coincident with the onset of menstruation, she noticed tingling and numbness in both lower extremities. Two days later she complained of weakness of the left half of her body and was not able to raise her left leg off the ground. She noticed that objects slipped from her left hand and that her grip was weak. On walking she tended to fall forward and would occasionally stumble in going up the stairs. On the morning of the day of her admission to the hospital she fell out of bed twice and noted altered sensation in the left half of her body and numbness and tingling in her left upper extremity.

The only abnormal findings on examination at the time of admission were those associated with left hemiparesis. There was moderate to pronounced weakness of all movements of the left extremities and of the lower portion of the left side of the face. The resistance of the left extremities to passive movement was increased slightly. The patient reported that pinprick was better perceived on the right side of the face and trunk and the right extremities than on the left side, and that pinprick on the left side felt definitely abnormal and "stingy." The left corneal reflex was reduced slightly. The deep reflexes were hyperactive, the exaggeration being slightly greater on the right side than on the left. The left abdominal reflexes were absent. The left plantar responses were of extensor type.

The pulse rate ranged around 90 per minute. The blood pressure was 138 systolic and 76 diastolic. The cerebrospinal fluid was completely normal; the Kahn reaction of the blood was negative. Examinations of the urine, stool and blood gave normal results. An electrocardiogram was interpreted as indicative of myocardial damage.

The patient remained in the hospital until September 10. Strength in the left extremities increased slightly during the five days in the hospital, but she never was able to walk without assistance, and she dragged her left foot along the floor.

The family noted that she was never able to return to work after her discharge from the hospital, on September 10, since the entire left side remained paretic. She could move her fingers and her left leg, but she could bear no weight on the latter; when she stood she had to hold on to something. In late October her left great toe would go into spasms of dorsiflexion and, according to the relatives, caused the patient considerable pain; she would scream during these episodes.

For a few days before her readmission to the General Hospital, in early November, she was delirious. The weakness, which had been limited to the left extremities and the left side of the face, spread to involve the right limbs a week or two before the readmission. She became unable to feed herself; and, though she could move the fingers slightly, she could not use her hands and was unable to lift either arm off the bed. About November 1 she became incontinent of stool and urine. She was readmitted to the hospital on November 5. At this time she was relatively unresponsive,

From the Laboratory of Neuropathology, Cincinnati General Hospital, and the University of Cincinnati College of Medicine.

1. Putnam, T. J.; McKenna, J. B., and Morrison, L. R.: Studies in Multiple Sclerosis: The Histogenesis of Experimental Sclerotic Plaques and Their Relation to Multiple Sclerosis, J. A. M. A. **97**:1591 (Nov. 28) 1931. Putnam, T. J.: The Pathogenesis of Multiple Sclerosis: A Possible Vascular Factor, New England J. Med. **209**:786, 1933; Evidence of Vascular Occlusion in Multiple Sclerosis and "Encephalomyelitis," Arch. Neurol. & Psychiat. **37**:1298 (June) 1937.

2. Scheinker, I. M.: Vasoparalysis of the Central Nervous System, a Characteristic Vascular Syndrome: Significance in the Pathology of the Central Nervous System, Arch. Neurol. & Psychiat. **52**:43 (July) 1944.

listless and dull. She seemed to recognize that questions were being asked and tried to answer, but she usually ended with stereotyped exclamations. At times she answered questions, but to most she gave fragmentary responses, and these were stereotyped; on some occasions she was considered to be aphasic. Speech was slurred. Sometimes she broke into laughter on being questioned. There was increased tone in all the extremities, particularly on the left side. She was occasionally able to move one extremity or the other, and it was determined that all the extremities were considerably weakened. There was weakness of the right lower part of the face. She could not sit up without support. It was practically impossible to test sensation. The deep reflexes were hyperactive. The abdominal reflexes were absent. There was bilateral forced grasping. The Hoffmann responses were obtained bilaterally, and the plantar responses were extensor, more obviously so on the left side.

On November 8 the patient used the correct words in singing songs, and she was able to move her upper extremities fairly well. For the most part her extremities rested in flexion and were spastic. Attempts to straighten a flexed extremity resulted in moans. Drooling of saliva was occasionally noted. Stertorous respiration, with a rate of 44 and an accompanying pulse with a rate of 140 per minute, made its appearance on November 11. Thereafter the temperature and respiratory rate, which had been relatively normal, rose steadily, and the patient refused nourishment. The neck and trunk became rigid. She was noisy at times and stuporous at others. After November 11 fluids had to be administered parenterally. She continued in an extremely precarious condition until November 16, when frequent convulsions were noted. Signs of lobular pneumonia made their appearance four or five days before death. She became comatose on November 13 and cyanotic on November 15, at which time she was placed in an oxygen tent. She died on November 17, seventy-four days after the initial symptoms of her illness.

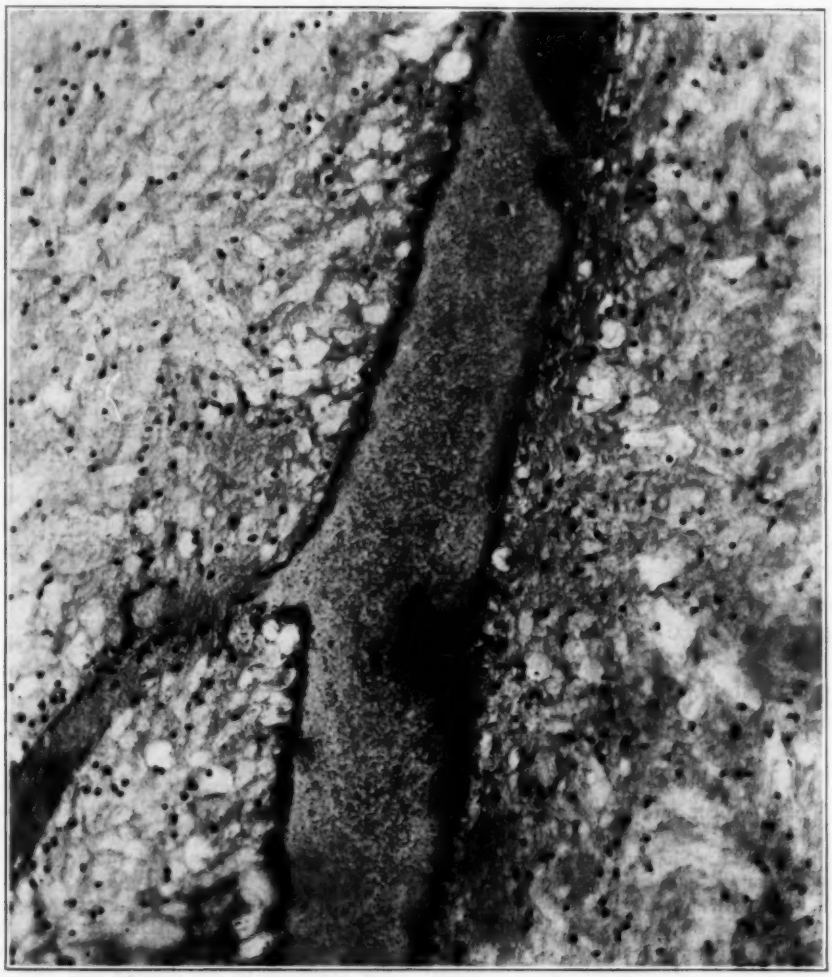

Fig. 1 (case 1).—Tremendously distended small vein, with signs of stasis. Note the beginning degeneration of the vessel wall and the early stage of edema and rarefaction of the surrounding tissue. Hematoxylin and eosin stain; × 225.

Autopsy.—The pathologic changes, exclusive of the lesions in the nervous system, were lobular pneumonia and fatty infiltration of the liver.

Examination of the nervous system was limited to the brain. The subarachnoid membrane showed slight brownish discoloration and moderate thickening. The meninges at the base were not remarkable. The configuration of the circle of Willis was normal, and the vessels did not disclose any gross alterations.

Coronal sections throughout the brain displayed obvious displacement of the ventricular system from the left to the right and widening of the white matter. The left cerebral hemisphere measured 7.2 cm. from the midpoint of the corpus callosum to its surface; the corresponding measurement for the right hemisphere was 4.9 cm. The basal ganglia on the left side appeared almost twice the size of those on the right. There was evidence of an intense and generalized congestion associated with numerous small petechial hemorrhages, throughout both the white and the gray substance, particularly noticeable in the swollen left hemisphere.

Microscopic Examination.—Sections were taken for survey from several areas of the gray and the white substance of both hemispheres and from the midbrain, pons and medulla. All sections were stained with hematoxylin and the Van Gieson stain, phosphotungstic acid hematoxylin, the Loyez stain for myelin sheaths and the Bodian 1 per cent strong protein silver method.

Histologic examination disclosed (1) vascular lesions and (2) alterations in the nerve tissue proper.

1. Vascular lesions. These consisted in maximal dilatation and congestion of the capillaries and small veins; they were engorged with blood and showed all the signs characteristic of vasoparalysis (fig. 1). In addition, many of the smaller blood vessels revealed degenerative changes or complete necrosis of the vessel wall, with increased permeability for serous fluid and red blood cells.

The most striking manifestation of the circulatory disturbances was the presence of early stages of thrombus formation, as illustrated in figures 2 and 3. The lumens of numerous small veins were completely occluded with blood clots, composed of curved strands of fibrin mixed with large masses of platelets and white blood cells. In some of the veins the clot seemed to be slightly attached to the intima. The vessel wall appeared well preserved except for slight loss of stainability of its cellular elements. Some of the veins contained only a relatively small number of fibrin threads, numerous platelets and a large mass of granular debris formed by broken-down white blood cells.

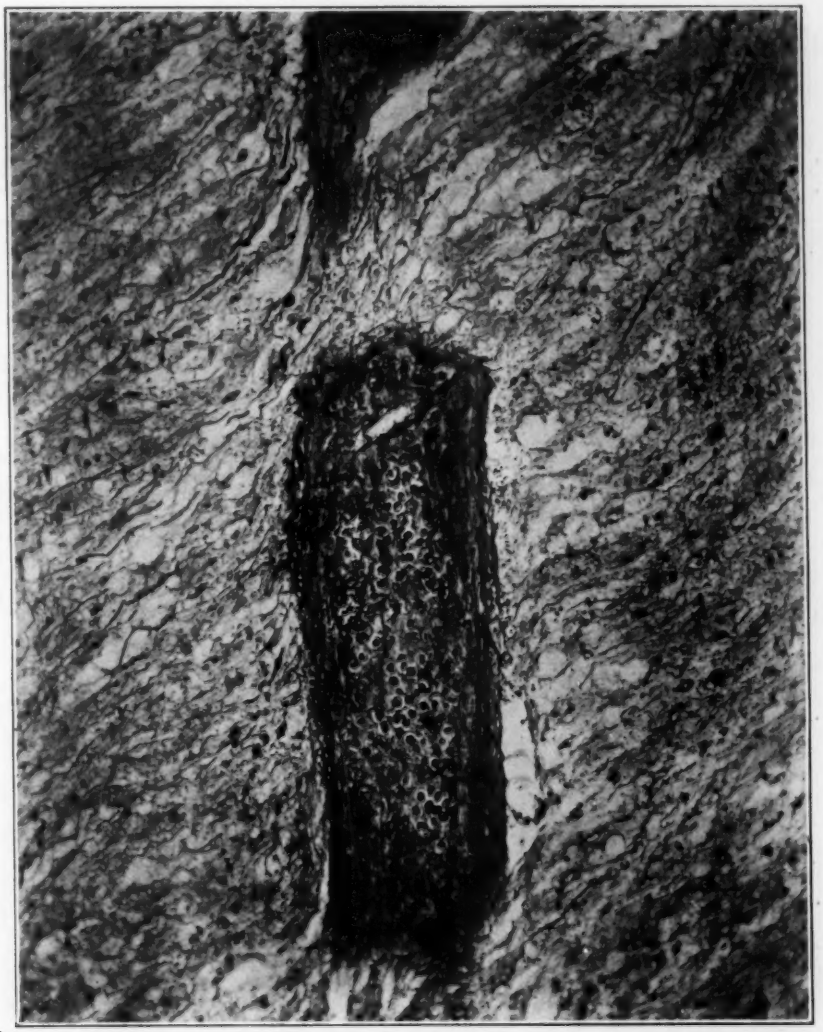

Fig. 2 (case 1).—Small vein completely occluded by a blood clot composed of large masses of platelets mixed with white blood cells and curved strands of fibrin. Note the tissue disintegration of the nerve parenchyma. Hematoxylin-eosin stain; × 225.

Late stages of thrombosis, such as organization with connective tissue, could not be seen. These various vascular lesions were noted throughout scattered areas of the brain and were more noticeable in the pial veins and the small vessels of the cortical ribbon, though present also in the subcortical white matter of the left hemisphere.

2. Changes in the nerve tissue proper, secondary, I believe, to the circulatory disturbances, consisted mainly of widely disseminated areas of softening involving the cortical ribbon and the white substance. A typical picture of the distribution of the lesions in the cortex is shown in figures 4 and 5. As can easily be seen, the areas of softening occupied the entire depth of the cortical gray matter. Most of the lesions stopped abruptly before the subcortical white matter was reached; in a few instances the latter was involved to a slight extent. Occasionally there were small, disseminated foci of softening in the white matter. The pia overlying the large cortical lesions was not thickened. It contained a great number of tremendously congested large veins. The cortex of the softened area showed several layers: First, there was a layer of dense glial reaction occupying the molecular zone, which was densely filled with glia cells, mostly astrocytes with large protoplasmic bodies and many processes. Some large veins perforated this layer. The entire deeper part of the cortical ribbon was completely destroyed and replaced by a large number of fatty granule cells and newly formed capillaries. The larger perforating vessels disclosed signs of stasis and were occasionally surrounded by thick sleeves of gitter cells. The process described was to be seen in almost all sections taken from several areas of the frontal, the parietal and the temporal cortex. In many instances the foci of softening were chiefly limited to one cortical layer, mostly the third. Many of the foci were circumscribed and small. The majority of the small foci suggested a perivascular distribution. In the central part of the lesion one or more small veins showed changes typical of vasoparalysis (fig. 6). In addition, there were disseminated areas of circumscribed glial scar formation (fig. 7).

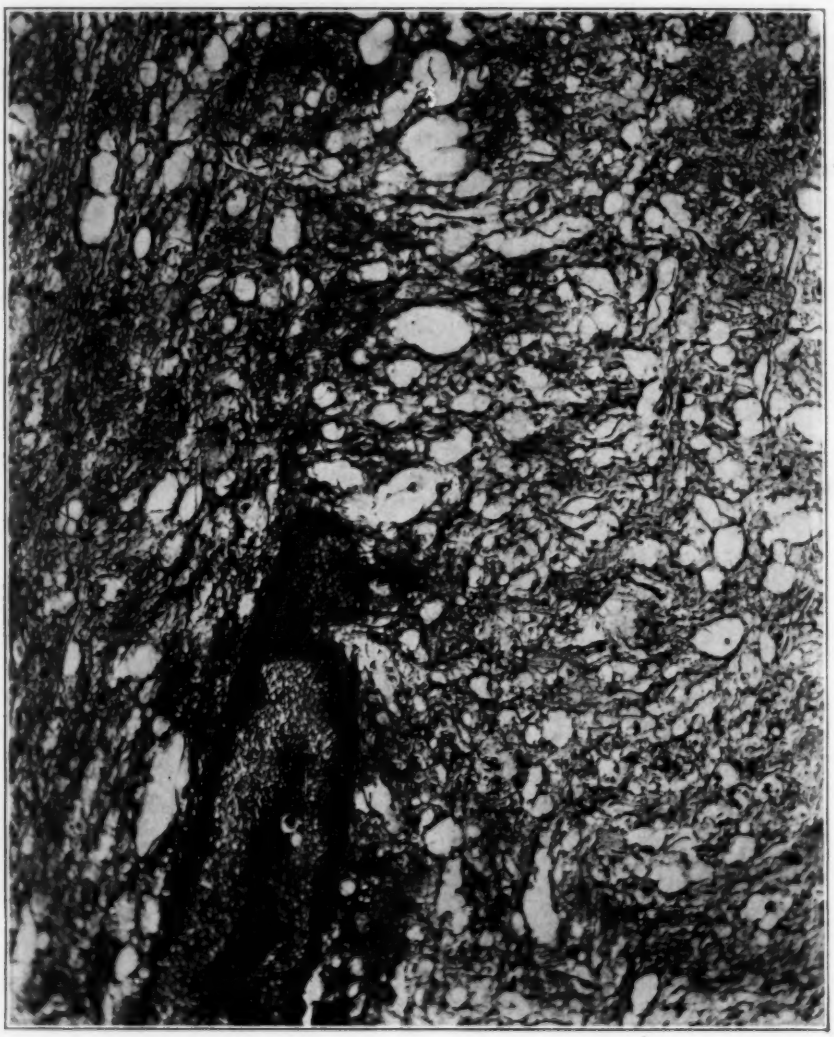

Fig. 3 (case 1).—Thrombosed vein surrounded by an area of tissue edema and necrosis. The blood clot is formed by a large mass of granular debris, fibrin threads and platelets.

Examination of the subcortical white matter disclosed changes typical of far advanced edema. The tissue showed an alveolar, sievelike appearance, with formation of numerous large vacuoles separated from one another by thin trabeculae. In some an early stage of tissue liquefaction could be seen. The nerve tissue appeared cellular because of the increase of swollen oligodendroglia cells. Most of the swollen glia cells showed regressive changes in the form of ameboid transformation. The bodies of some of the cells showed increase in size and conspicuous degeneration associated with a typical picture of clasmatodendrosis, indicative of a far advanced destructive process. In addition, many veins and capillaries were tremendously distended, displaying the characteristic signs of stasis.

Sections taken from the deeper parts of the centrum semiovale exhibited a diffuse swelling of all tissue elements. In addition there was a slight degree of tissue rarefaction. The swelling of the nerve fibrils is illustrated in figure 8. There were many transitional areas between the relatively early stage of swelling of the brain and the more advanced changes described as edema.

Summary.—The most striking feature in this case consisted of numerous, diffusely circumscribed areas of softening scattered throughout the central nervous system. The lesions were characterized histologically by a patchy distribution and by an ischemic type of tissue destruction. These features suggest that the lesions were of circulatory origin, although there were no demonstrable structural changes in the vessel wall in the related meningeal and cortical vessels. Within the focal lesions the blood vessels disclosed a far advanced stage of vasoparalysis, alternating with early stages of thrombus formation.

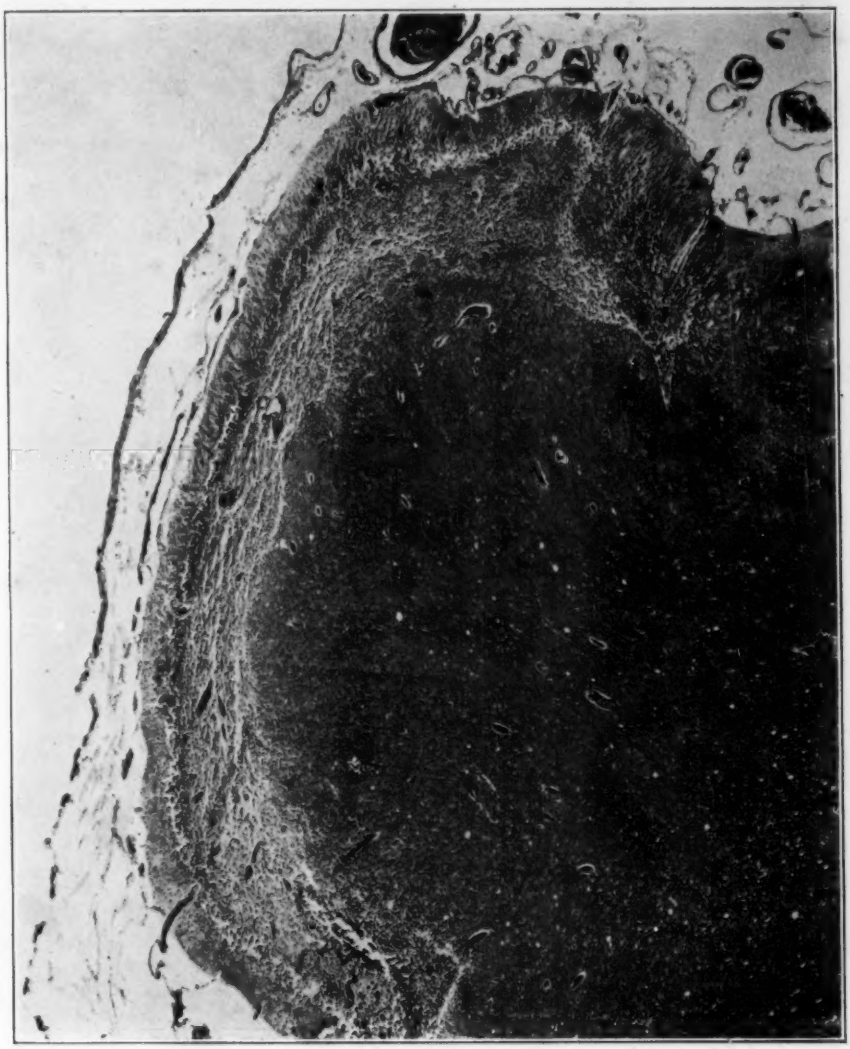

Fig. 4 (case 1).—A widely disseminated area of softening involving the cortical ribbon. Hematoxylin-eosin stain; × 35.

Case 2.—A white man aged 63 was admitted to the hospital on June 4, 1943, with the complaint of slight clumsiness of the right arm, incoordination in walking and some delay and thickness of speech. Little in the

past history appeared to be relevant. Several weeks before his entrance to the hospital he misstepped in going downstairs and jarred himself rather severely.

On admission the temperature was 98 F., the pulse rate 68, the respiratory rate 19 and the blood pressure 220 systolic and 110 diastolic. Neurologic examination revealed that he was well developed and well nourished, but obviously dysphasic. His speech rambled, and he used improper words at times. He followed verbal commands fairly well. He had difficulty in reading headlines but was able to write to dictation fairly well.

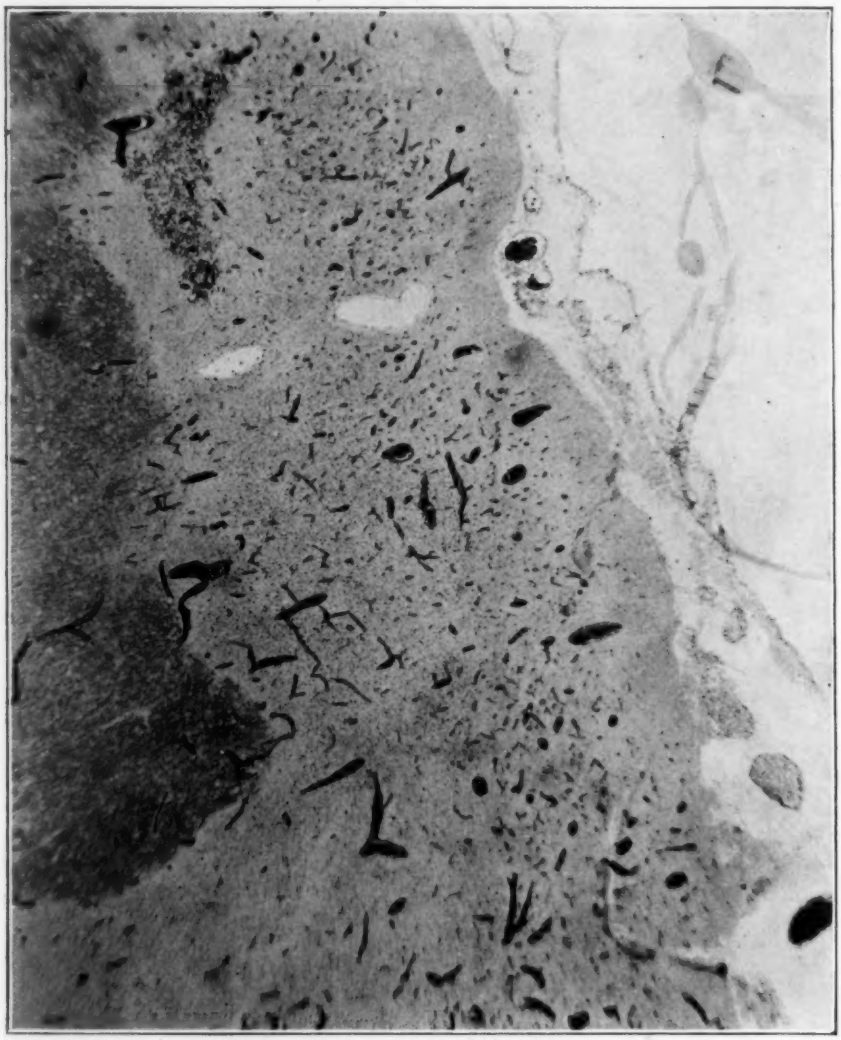

Fig. 5 (case 1).—A large area of cortical softening. Note the large number of congested and partly occluded veins. Loyez stain for myelin sheaths; × 45.

Auscultation of the head revealed nothing significant. There was no evidence of head injury. The visual fields and fundi were normal. The pupils were equal, each measuring 3 mm., and reacted well to light. Extraocular movements were normal. There was slight ptosis of the right eyelid. The corneal reflexes were active bilaterally. There was definite weakness of the right side of the face. The appearance of the pharynx and tongue was not remarkable.

Motor power of the right arm and leg was decreased. All deep reflexes were hyperactive; there was ankle clonus bilaterally, and a questionable Babinski sign was elicited on the right. No abnormalities of coordination were detected. All forms of sensation, including position and stereognostic senses, were normal.

A lumbar puncture was performed on June 6. The initial pressure was 75 mm. of water; the fluid was clear and colorless and contained 3 lymphocytes per cubic millimeter and no red cells. On October 12 the patient died.

Autopsy.—Autopsy was performed two and a half hours after death. The pathologic conditions exclusive of the lesions in the nervous system were focal myocardial fibrosis and terminal pulmonary congestion.

Examination of the nervous system was limited to the brain, which weighed 1,350 Gm. All the superficial veins showed diffuse congestion. The blood vessels at the base had a normal distribution and exhibited a moderate degree of arteriosclerosis. Coronal sections through both hemispheres displayed numerous, diffusely scattered areas of tissue destruction, involving both the white and the gray matter. The medulla and the pons appeared normal.

Microscopic Examination.—In general histologic examination of sections taken from various areas of both hemispheres confirmed the gross observations and revealed changes were almost identical with those described in the first case. The greater part of the cortical ribbon was "moth eaten" with numerous small areas of tissue softening. These lesions varied in size and shape; many of them were small perivascular foci restricted to an area surrounding a small vein or a group of capillaries (fig. 9). Others were somewhat larger, involving almost an entire convolution. At times they coalesced and thus assumed a pseudolaminar pattern; they produced an irregular mottled, distorted appearance of the cortical ribbon.

The histologic details were not quite uniform in all the lesions. In figure 10 is shown an area of circumscribed tissue destruction in which the entire nerve parenchyma was transformed into a large accumulation of fat granule cells. In sections stained with scarlet red, large lipid deposits were seen within the fat granule cells and in the perivascular tissue.

While these lesions represented the most frequent type of tissue destruction, focal areas of gliosis were diffusely scattered throughout the gray and the white matter. These areas were characterized by an accumulation of astrocytes and represented glial scar formation.

In almost all lesions the small blood vessels (chiefly veins) and capillaries were conspicuous because a tremendous degree of stasis and early stages of thrombus formation were present. The vascular changes were almost identical with those described in the first case; their detailed description will therefore be omitted. They are illustrated in figures 9, 10, 11 and 12. It is of interest, however, to note that thrombus formation was most frequently observed in lesions in which early changes were present; they were seldom seen in older lesions characterized by glial scar formation. The vessel wall of the smaller blood vessels did not disclose any signs of an organic vascular process. Only very few of the larger blood vessels revealed a moderate degree of arteriosclerosis.

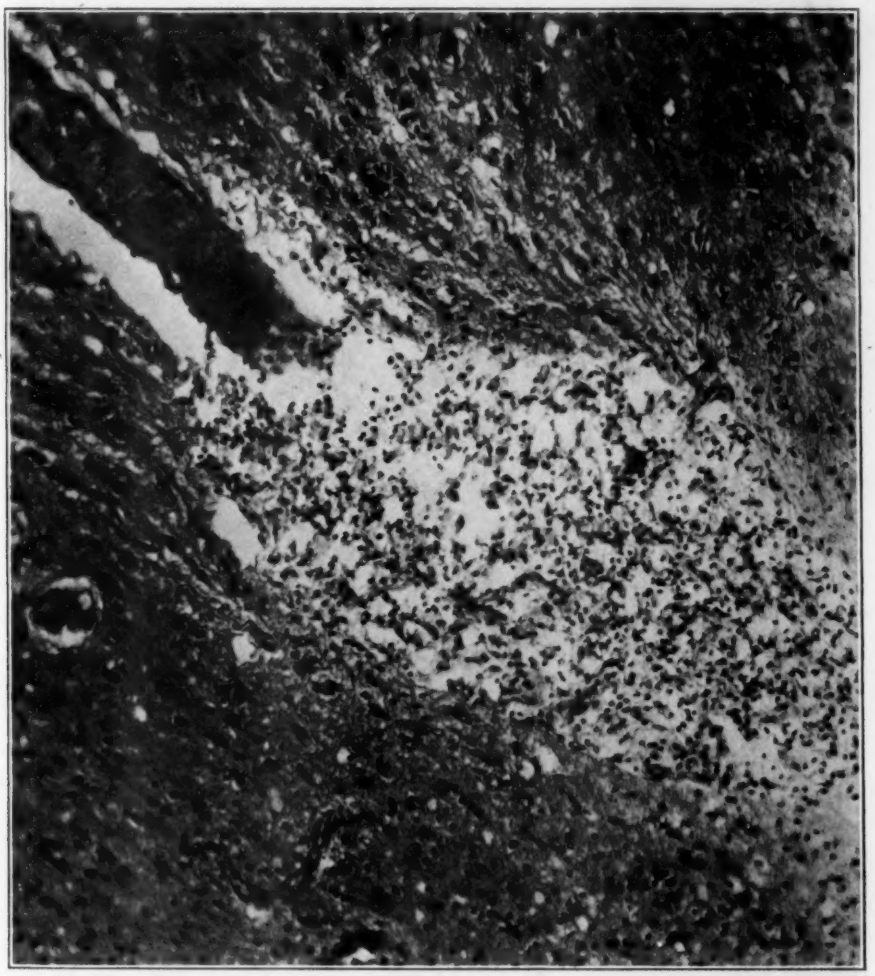

Fig. 6 (case 1).—Small circumscribed area of softening. Note the tremendously distended vein. Hematoxylin-eosin stain; × 135.

The leptomeninges were slightly thickened and distended and contained red blood cells and gitter cells. The pial blood vessels were distended and engorged with blood and were surrounded with large accumulations of extravasated blood. Their vessel walls appeared normal.

SUMMARY OF PATHOLOGIC CHANGES

The microscopic changes in both cases consisted of widely disseminated areas of softening, usually perivascular in distribution. The areas

of tissue destruction were characterized by almost complete transformation of the nerve parenchyma into compound granule cells harboring lipids and blood pigment. It should be emphasized that lack of structural changes in the vessel wall formed a striking feature of the histologic process. Neuropathologists will recognize at once that the disseminated lesions corresponded in all their details with lesions which are considered characteristic of softening of the brain tissue, of vascular origin, as frequently observed in cases of thrombosis due to arteriosclerosis, syphilis or other organic vascular disease. Attention is called to the striking fact that none of all the commonly known factors producing thrombosis could be detected. The predominant vascular alterations consisted in congestion, stasis and vasoparalysis and were associated with thrombus formation, chiefly confined to the smaller veins and capillaries. As has been demonstrated in illustrations, many of the smaller blood vessels were tremendously dilated and completely occluded with curved strands of fibrin mixed with large accumulations of platelets. In addition to the venous occlusion, histologic examination revealed in both cases a definite type of vascular alteration, which has been recently described under the heading of vasoparalysis.[2] The morphologic criteria for this vascular syndrome were listed as follows: (1) maximal distention and engorgement of the smaller veins and capillaries, (2) signs of stasis, consisting in hemolysis of red blood cells, (3) degenerative changes or complete necrosis of the vessel wall, with increased permeability for serous fluid and red blood cells and (4) distention of the perivascular spaces, which usually contain extravasated serous fluid and red blood cells.

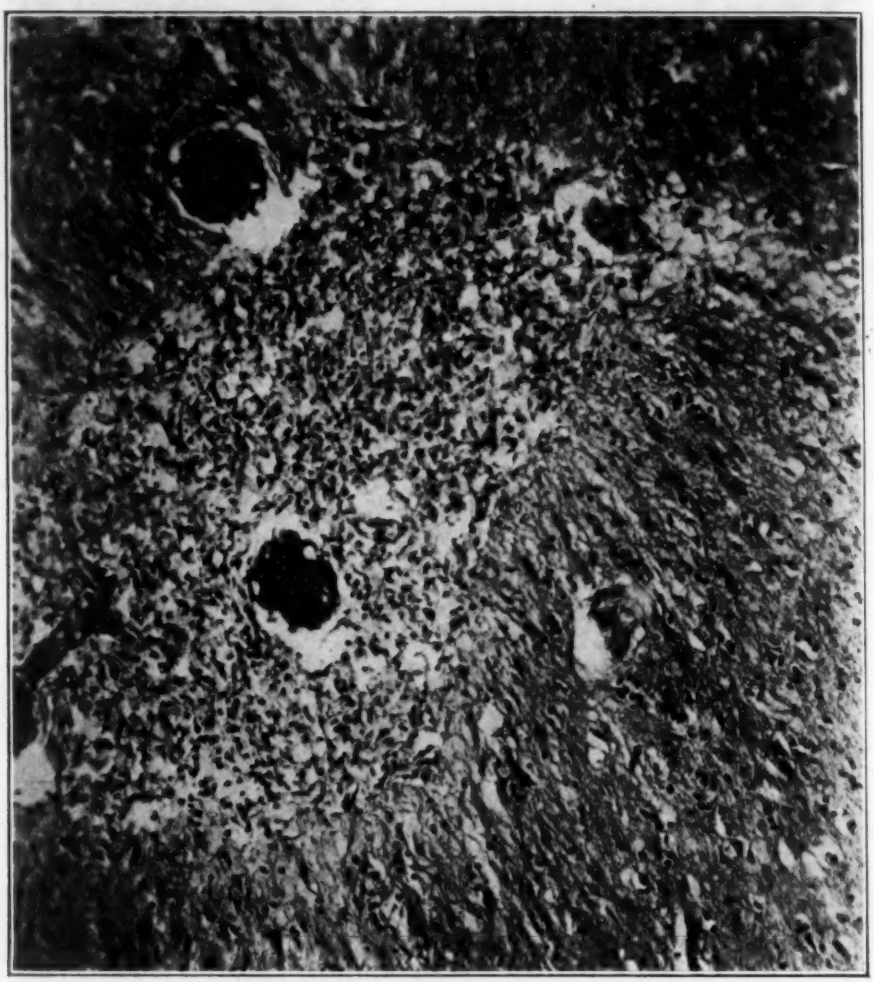

Fig. 7 (case 1).—Small area of tissue softening, with an early stage of glial replacement. Note the congested veins, with signs of vasoparalysis. Hematoxylin-eosin stain; × 135.

DIFFERENTIATION OF THE VASCULAR ALTERATIONS IN THIS SYNDROME AND THOSE IN ACUTE VASOPARALYSIS

In spite of the morphologic resemblance of the reported changes to the alterations described as characteristic of acute vasoparalysis, there were indications that some differences exist between the two conditions. These may be summarized as follows: In cases of acute vasoparalysis an increased permeability of the vessel wall for serous fluid and red blood cells, resulting in multiple petechial hemorrhages and edema, was the most striking and the predominant feature. In the vascular lesions in the cases reported here these changes were observed only occasionally and were of no great significance. The most striking feature was the presence of thrombus formation in many of the tremendously distended veins and capillaries, as illustrated in figures 2, 3, 11 and 12. Whereas the alterations in the nerve tissue in the cases of acute vasoparalysis consisted mainly of scattered small areas of petechial hemorrhages and edema, in the present cases they were represented by disseminated foci of tissue destruction consisting of recent and old areas of softening. The presence of these small foci of tissue necrosis contiguous to the occluded veins and capillaries indicates that these tissue changes were secondary to the vascular alterations.

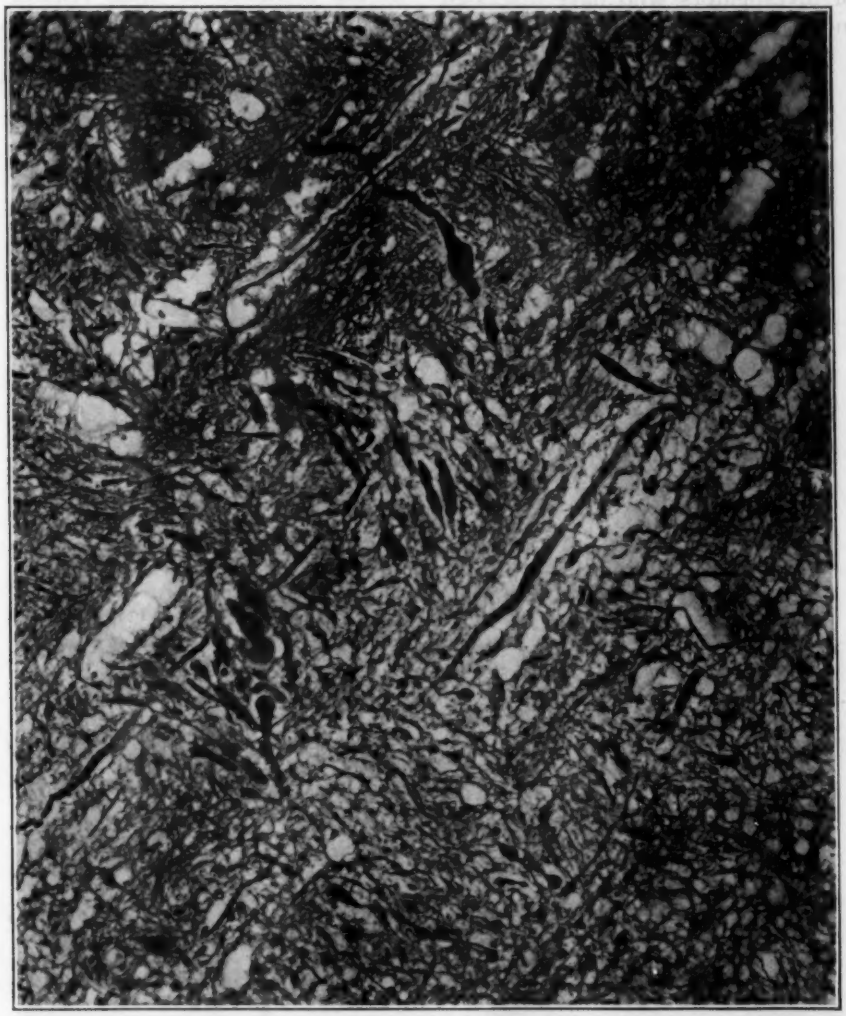

Fig. 8 (case 1).—Pronounced swelling of the axis-cylinders and tissue rarefaction. Bodian method of silver impregnation; × 225.

From these points of differentiation it seems proper to conclude that the vascular alterations under discussion should be separated from the vascular lesions of acute vasoparalysis as a special vascular syndrome, under the heading of "vasothrombosis of the central nerve system." It should be emphasized, however, that the vasothrombosis must be considered as a late sequela

of acute vasoparalysis. Both vascular syndromes, the acute vasoparalysis and the vasothrombosis, are phases of the same morbid process. The difference in their morphologic features can probably be explained by the difference in the duration and severity of the same morbid process.

DEFINITION OF VENOUS THROMBOSIS

The list of investigators who have discussed the significance of venous occlusion in disseminated sclerosis is long. There is no need to give in detail the controversy concerning this problem. My personal experience and point of view have been reported elsewhere.[3]

It is my impression that a great deal of confusion is created by the lack of a clearcut definition of the morphology of thrombosis. This is particularly true with respect to the thrombotic occlusion of smaller blood vessels, especially veins. Most descriptions in the textbooks are based on the study of thrombosis of large arteries. The morphologic feature characteristic of the occlusion of small venules is not compatible with the generally accepted conception of thrombosis of the larger arteries. The consensus among pathologists is that a pathologic state of the vessel wall caused by arteriosclerosis, syphilis or other pathologic process is necessary for the formation of a thrombus. This might be correct for the thrombotic occlusion of the smaller veins. The observations reported in this study, as well as those described by Putnam,[1]

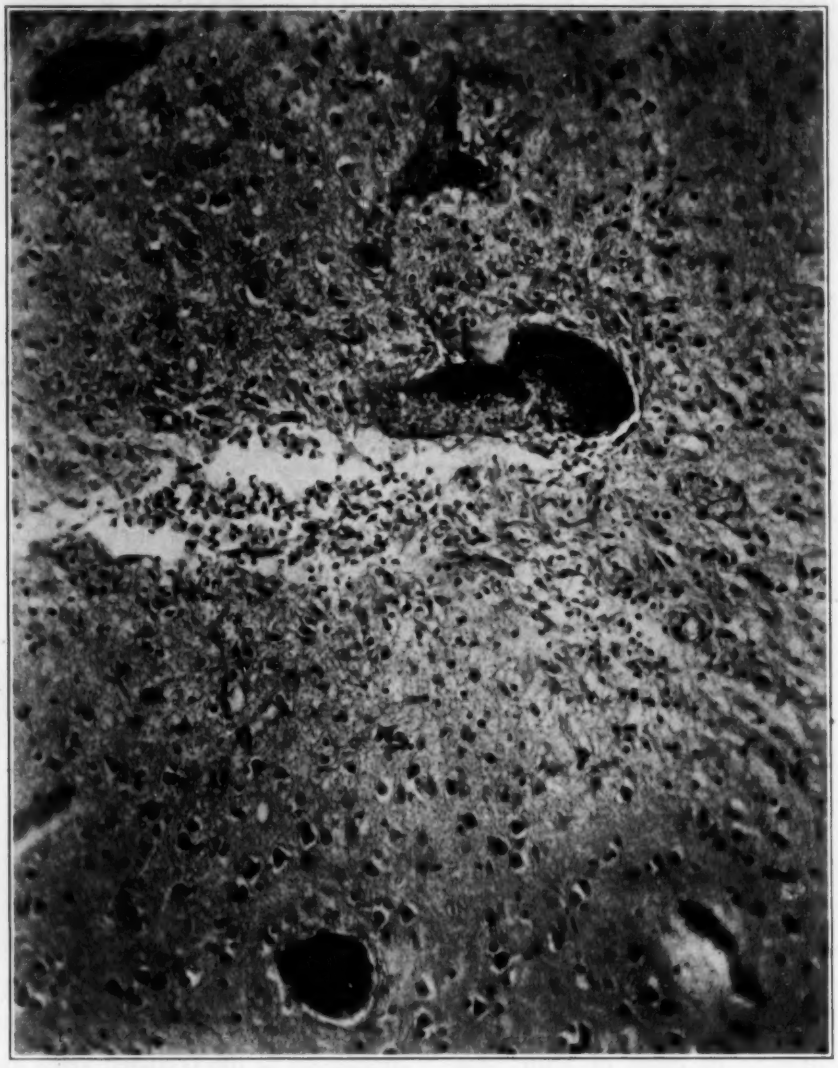

Fig. 9 (case 2).—A small area of softening in the vicinity of a vein displaying an early stage of occlusion. Hematoxylin-eosin stain; × 165.

3. Scheinker, I. M.: Histogenesis of the Early Lesions of Multiple Sclerosis: Significance of Vascular Changes, Arch. Neurol. & Psychiat. **49**:178 (Feb.) 1943.

have demonstrated the occurrence of venous occlusion in healthy blood vessels. Recent investigations made by Stuber and Lang [4] have indicated that the production of certain chemical changes in the blood may cause clotting in intact blood vessels.

What are the morphologic criteria of venous thrombosis? In the older literature on thrombosis the chief criterion of a thrombus was the presence of an organized blood clot adherent to the vessel wall. This definition is not applicable to venous occlusion, for the following reason: As has already been stated, it is generally admitted that injury to the intima, that is, a pathologic state of the vessel wall caused by arteriosclerosis, syphilis or other organic lesion, is the main factor in the origin of arterial thrombosis. The injured intima facilitates the adherence of the blood clot to the arterial wall in the very beginning of the process. In venous occlusion the thrombus formation usually takes place in healthy vessels with a well preserved endothelial lining of the lumen. Under these circumstances adherence of the clot to the vessel wall cannot be expected, at least not in the early stage. It is therefore my impression that the mere presence of clots of an amorphous mass of agglutinated red blood cells associated with a large accumulation of platelets and large curved strands of fibrin which plug completely the lumen of an enormously distended small venule or capillary is sufficient evidence of venous thrombosis. If these changes are associated with secondary

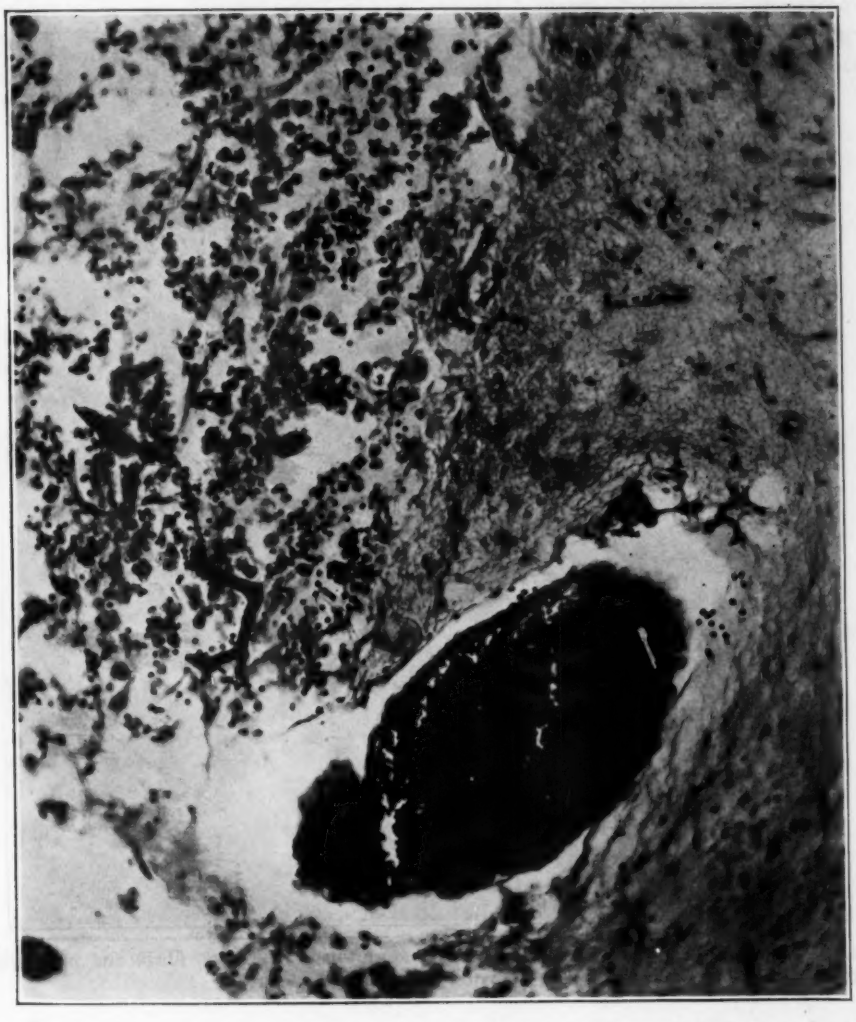

Fig. 10 (case 2).—Circumscribed area of tissue softening, with a large accumulation of fat granule cells. Note the tremendously distended and occluded vein. Hematoxylin-eosin stain; × 135.

4. Stuber, B., and Lang, K.: Die Physiologie und Pathologie der Blutgerinnung, Berlin, Urban & Schwarzenberg, 1930, pp. 74-78.

lesions of the adjacent nerve tissue, typical of vascular occlusion and perivascular in distribution, there is little doubt that the venous occlusion ought to be regarded as thrombotic. Such alterations can scarcely be confused with clot formations after death.

Of great theoretic and practical interest is the problem of subsequent development of venous thrombosis. In cases of arterial occlusion it is quite evident that within a few days or less definite signs of organization can be expected; gradual transformation into a fibrous plug, with or without final recanalization, is the usual end stage of an arterial thrombus. What is the subsequent development of a venous thrombus? According to Putnam,[1] it is conceivable that thrombosed small veins may after a certain period disintegrate completely, redissolve and be no longer recognizable. Experimental evidence for such a possibility has been given by Kusama.[5]

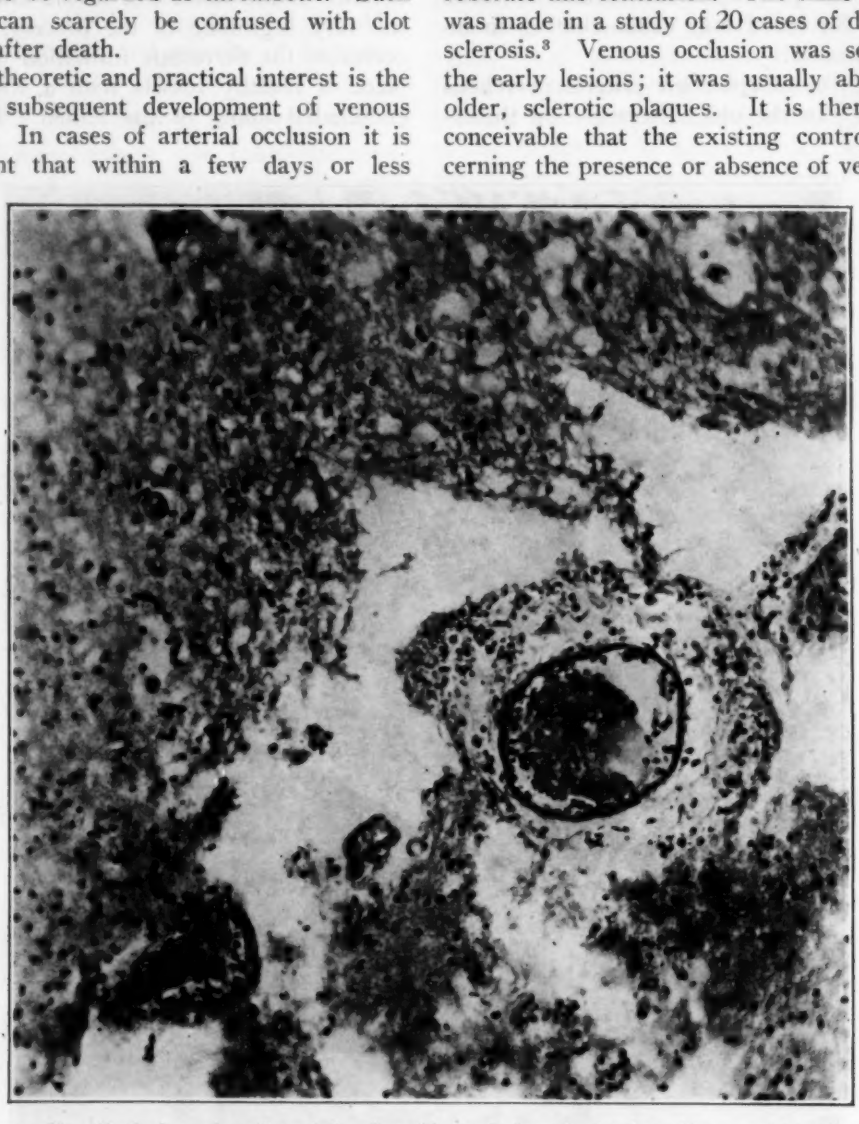

Fig. 11 (case 2).—Occlusion of a distended vein with agglutinated platelets, fibrin and blood pigment. Note the disintegration of the surrounding tissue. Hematoxylin-eosin; × 165.

The fact that in my cases thrombus formation was observed mainly in early lesions and was seldom seen in foci of gliosis seems to corroborate this conclusion. The same observation was made in a study of 20 cases of disseminated sclerosis.[3] Venous occlusion was seen only in the early lesions; it was usually absent in the older, sclerotic plaques. It is therefore quite conceivable that the existing controversy concerning the presence or absence of venous occlusion in cases of disseminated sclerosis is based on the fact that the conclusions of most of the investigators were drawn from observations on old, sclerotic plaques, where the previously thrombosed veins were possibly disintegrated and no longer recognizable.

TENTATIVE EXPLANATION OF THE PATHOGENESIS OF VENOUS OCCLUSION

The present study has brought out the fact that thrombus formation may develop in healthy blood vessels in which there is no indication of a primary cause of thrombosis in the vessel wall

5. Kusama, S.: Ueber Aufbau und Entstehung der toxischen Thrombose und deren Bedeutung, Beitr. z. path. Anat. u. z. allg. Path. **55**:459, 1913.

itself. Thus it would appear that the pathogenic mechanism might be expected to be present in the blood stream. What conditions in circulating blood itself or in the blood flow may lead to venous thrombosis?

According to Putnam,[1] the primary abnormal factor in venous occlusion in cases of multiple sclerosis is to be sought in the clotting mechanism of the blood.

It is my impression that the decrease in the rate of cerebral circulation ought to be considered one of the principal factors which generally favor the occurrence of venous occlusion. As has been brought out in previous papers, the state of vasoparalysis is always associated with extreme dilatation of the smaller veins and with signs of stasis characterized by hemolysis of the red blood cells. Thus, the tremendous vascular distention, together with a considerable slowing down of the blood flow, is apparently the most frequently observed factor contributing to the formation of venous thrombosis.

In support of this conception the following points may be marshaled: Zahn [6] was one of the first to demonstrate in a series of experiments that thrombosis sufficient to close the vessel occurred only in the presence of a very weak stream; in a stream of normal speed only a partial "separation" of the blood took place.

Eberth and Schimmelbusch,[7] repeating the experiments of Zahn, concluded that mechanical changes in the blood stream are as essential for thrombosis as is injury to the wall of the blood vessel. Beneke,[8] observing the streaming blood, emphasized that when partial obstruction is produced in the blood stream, there is developed peripheral to the obstruction a small whirlpool. Into this platelets are collected and held. The same phenomenon was observed when there was a sudden widening of the blood stream.

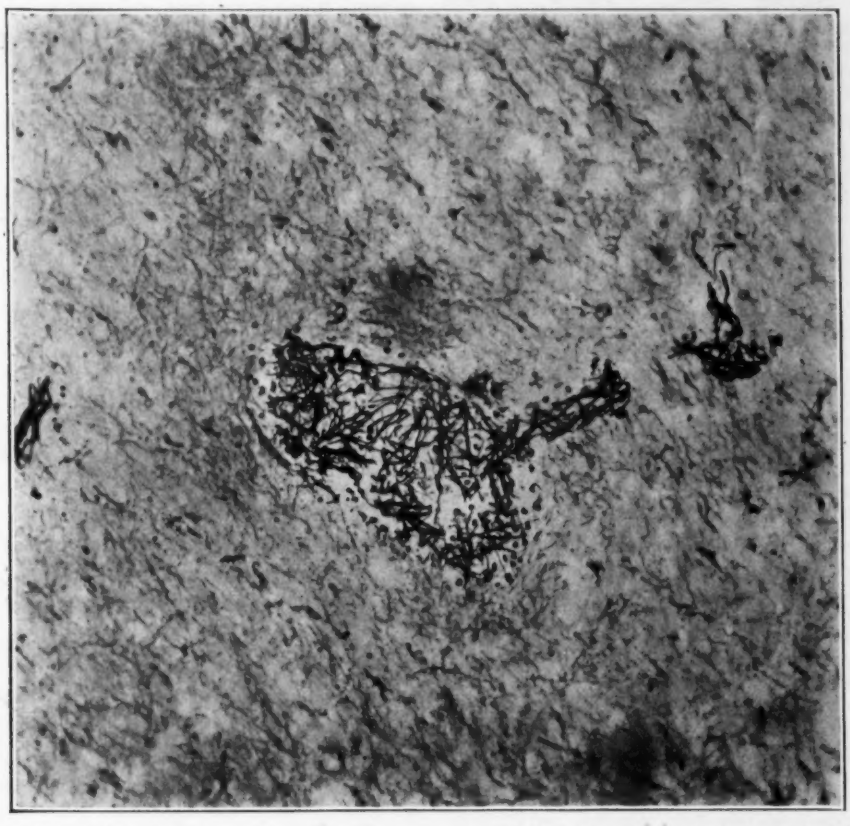

Fig. 12 (case 2).—Occlusion of a vein, with a large number of curved strands of fibrin. Phosphotungstic acid stain; ×165.

6. Zahn, W.: Untersuchung über Thrombose: Bildung der Thromben, Virchows Arch. f. path. Anat. **62**:81, 1875.

7. Eberth, J. C., and Schimmelbusch, C.: Experimentellé Untersuchungen über Thrombose, Virchows Arch. f. path. Anat. **53**:39, 1886.

8. Beneke, R., in Krehl, L., and Marchand, F.: Handbuch der allgemeinen Pathologie, Leipzig, S. Hirzel, 1913, vol. 2.

From these experimental data one may conclude that the formation of a thrombus in smaller veins may be considerably favored by partial immobilization of the blood stream.

SUMMARY

1. In 2 cases in which the smaller veins and capillaries were filled with blood clot the occlusion is interpreted as being due to local slowing down of the circulation.

2. The earliest manifestation of the pathologic process is vasoparalysis of the central nervous system.

3. The venous occlusion is apparently a late sequel of a prolonged state of vasoparalysis.

4. "Vasothrombosis" and vasoparalysis are to be considered phases of the same morbid process. The difference in their morphologic features can be explained by the difference in the duration and severity of the pathologic process.

Cincinnati General Hospital.

POLYRADICULONEURITIS WITH ALBUMINOCYTOLOGIC DISSOCIATION

PATHOANATOMIC REPORT OF THREE CASES

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A multiple neuritis of unknown origin characterized by its frequent association with infection of the respiratory tract, increased protein in the spinal fluid without an increase in the cell content, frequent involvement of cranial nerves and a benign course was described by Guillain, Barré and Strohl[1] in 1916. The clinical distinction between this syndrome and other neuritides, frequently designated as Landry's paralysis (acute ascending myelitis), peripheral neuritis with facial diplegia, acute infective polyneuritis, acute febrile polyneuritis, infective neuronitis, acute ascending paralysis and myeloradiculitis, is not sharply defined (De Jong[2]).

No pathologic anatomy was described either in the original or in subsequent observations of Guillain,[3] who insisted on a uniformly favorable outcome as an essential diagnostic criterion. However, pathoanatomic reports with emphasis on the peripheral nervous system are available of the same disease, or at least of closely allied disorders, but little is known of the condition of the central nervous system. We wish to report 3 fatal cases of this illness with extensive changes in the spinal cord and brain stem.

REPORT OF CASES

CASE 1.—W. N., a man aged 22, a factory worker, had a sudden onset of severe abdominal pain with nausea and vomiting on Oct. 18, 1941. These symptoms were interpreted as those of appendicitis. However, appendectomy failed to bring relief; four days later, with spinal anesthesia, the entire abdominal cavity was explored, without evidence of any abnormalities. Roentgenographic and bacteriologic examinations of the gastrointestinal tract revealed nothing significant. The abdominal symptoms disappeared gradually. Five weeks later there developed a sore throat, followed by pain, weakness and numbness of all four extremities and rapid progression to complete tetraplegia. There were also transient hoarseness and weakness of the muscles of the left side of the face, with inability to close the eye. The patient was admitted to the hospital ten weeks after onset of the symptoms.

Examination.—There were bilateral paresis of the muscles of mastication; bilateral facial palsy of peripheral type, more pronounced on the left side; unilateral paresis of the recurrent laryngeal nerve; paresis of the tongue; mild dysphagia, and complete flaccid tetraplegia, with advanced muscular atrophy in all four extremities. Slight voluntary movements were preserved in the spinal, intercostal and abdominal muscles; the function of the diaphragm was normal. All superficial and tendon reflexes were absent. The sense of motion and position was lost, and vibratory sensation was diminished in all four extremities, together with distal blunting of all modalities of superficial sensation. The optic nerves, pupillary reactions, extraocular muscles and auditory nerves showed no disturbance; the muscles and nerve trunks were not tender, and signs of meningeal irritation were absent. There was an area of consolidation in the upper lobe of the right lung.

Laboratory Examination.—The urine was normal; the Kahn reaction of the blood was negative, and no Klebs-Loeffler bacilli were present on culture of material from the throat. The hemoglobin concentration was 90 per cent (Sahli); the red blood cell count was 4,900,000 per cubic millimeter; the white blood cell count ranged from 5,000 to 14,000 cells per cubic millimeter, and blood films showed no stippling of cells. The cerebrospinal fluid was under normal pressure. There were 7 cells per cubic millimeter, and the Pandy and Nonne-Apelt reactions were positive. The Kahn reaction of the spinal fluid was negative; the colloidal gold curve was 0001221100, and the total protein content was 400 mg. per hundred cubic centimeters. Blood cultures yielded no growth; no lead or abnormal pigments were found in the urine. Roentgenograms revealed an abscess in the upper lobe of the right lung.

Course in the Hospital.—The pulmonary infection grew steadily worse, and the patient died eighty-five days after onset of the neurologic symptoms.

Pathoanatomic Examination.—Peripheral Nerves: There was advanced degeneration of the myelin sheaths, numerous bundles of which had lost their normal structure and appeared almost amorphous in azan preparations; such bundles were greatly swollen, their diameter being five to six times that of the normal. The axis-cylinders were swollen and fragmented, and their number was greatly reduced. The Schwann cells were increased in size and number. Marchi preparations contained numerous myelin fragments (fig. 1).

Read at the Seventieth Annual Meeting of the American Neurological Association, New York, May 20, 1944.

From the Neuropathology Laboratory of the Neuropsychiatric Institute, and the Department of Neurology, University Hospital and the University of Michigan Medical School.

1. Guillain, G.; Barré, J. A., and Strohl, A.: Sur un syndrome de radiculo-névrite avec hyperalbumose du liquide céphalo-rachidien sans réaction cellulaire, Bull. et mém. Soc. méd. d. hôp. de Paris **40**:1462 (Oct. 13) 1916.

2. De Jong, R. N.: The Guillain-Barré Syndrome, Arch. Neurol. & Psychiat. **44**:1044 (Nov.) 1940.

3. Guillain, G.: Radiculoneuritis with Acellular Hyperalbuminosis of the Cerebrospinal Fluid, Arch. Neurol. & Psychiat. **36**:975 (Nov.) 1936.

Posterior Root Ganglia: The parenchymal cells of the peripheral ganglia showed outspoken axonal degeneration (fig. 2).

Central Nervous System: Most information was obtained from the Marchi sections, which demonstrated severe degeneration of the white matter in all columns of the spinal cord and in numerous systems as far as the thalamus. The fasciculus gracilis and fasciculus cuneatus were laden with Marchi bodies (fig. 3). There was also severe degeneration of the spinocerebellar pathways and the pyramidal and rubrospinal tracts. The same picture prevailed throughout the spinal cord and continued into the medulla. The fibers of the medial lemniscus contained large masses of myelin fragments, so that the bundles were sharply outlined (fig. 4); the fibers of the hypoglossus nerve stood out distinctly, being heavily laden with myelin fragments (fig. 4). There were similar severe changes in the olivocerebellar fibers and in the fibers of the reticulate substance, as well as in the intrabulbar portion of the fibers of the fifth, eighth, ninth and tenth nerves. The degeneration was less severe in the tectospinal tract and in the medial longitudinal fasciculus. The external arcuate fibers were not degenerated.

In Nissl preparations axonal degeneration was outspoken in the lumbar and sacral segments of the cord, particularly in the dorsolateral nuclei of the anterior horns; shrunken, deeply staining neurons could be seen in the higher segments of the spinal cord and in the brain stem as far as the midbrain. The basal ganglia, the cortex, the cerebellum and the meninges showed no pathologic changes.

Fig. 1.—Photomicrograph of section of a peripheral nerve, showing numerous fragments of degenerated myelin (black). Marchi method; Zeiss planar lens, 20 mm.

Case 2.—E. P., a truck driver aged 21, was admitted to the University Hospital on March 28, 1941. Three weeks previously he noted numbness in the feet, which soon became paralyzed, progressive weakness in the hands, double vision and pain in the back of the head. There was no history of antecedent infection.

Examination.—Examination revealed paralysis of the left lateral rectus muscle and palsy of the left side of the face of peripheral type; flaccid tetraparesis with proximal predominance; bilateral diminution of the biceps reflex, with absence of the remaining deep tendon reflexes; normal cremasteric and abdominal reflexes, and an extensor plantar response on the right side, with an equivocal extensor plantar response on the left side. There were mild dyspnea, dysarthria and dysphagia, mild paresis of the abdominal and intercostal muscles and moderate paresis of the deep spinal muscles. Vibratory sensation and the sense of position were notably diminished in the lower extremities and moderately diminished in the upper extremities. Superficial sensation was preserved except for diminished pain and tactile sense in a radicular pattern corresponding to the upper lumbar dermatomes. The muscles and nerve trunks were tender to palpation, and there were mild nuchal rigidity and a faint Kernig sign.

Laboratory Examinations.—The urine was normal. The Kahn reaction of the blood was negative. There were 14,000 white blood cells per cubic millimeter, with variations from 6,000 to 22,000 cells. The blood was otherwise normal. The cerebrospinal fluid was clear and colorless, contained no cells and was under normal pressure; the Kahn reaction of the fluid was negative, and the colloidal gold curve was normal. The Pandy and Nonne-Apelt reactions were positive; the total protein content was 105 mg. per hundred cubic centimeters.

Course in the Hospital.—Increasing weakness of the respiratory muscles complicated with pneumonia required treatment in the Drinker respirator from the third to the twenty-fourth day of hospitalization. The pneumonia responded to treatment with sulfadiazine and oxygen, and the patient was removed from the respirator. However, twelve days later the respiratory difficulties increased; the pulmonary infection became grave, and death occurred on the sixty-fifth day after the onset of the symptoms.

Pathoanatomic Examination. — Peripheral Nerves: Degeneration was of the same type as that in the preceding case.

Posterior Root Ganglia: There was outspoken axonal degeneration.

Central Nervous System: Marchi preparations disclosed large accumulations of black myelin fragments in the white matter of the spinal cord, particularly in the fasciculus gracilis and fasciculus cuneatus (fig. 5).

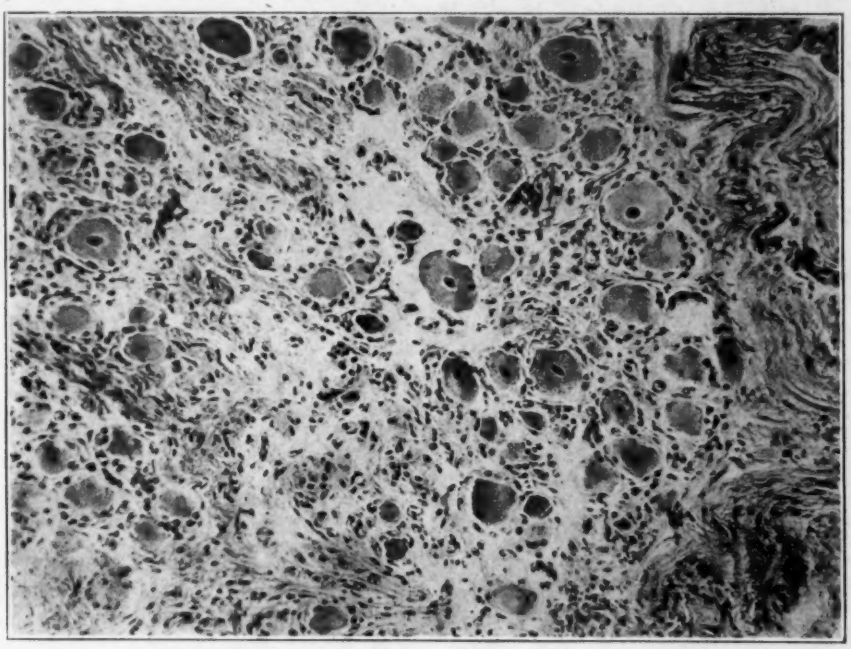

Fig. 2.—Photomicrograph showing axonal degeneration (posterior root ganglion). Azan stain; objective (Zeiss) × 20; ocular, projection 2.

The parenchyma showed a variety of degenerative changes. There was outspoken axonal degeneration in the lumbosacral segments, but not elsewhere in the central nervous system. In the higher segments of the cord, the medulla and the midbrain, the dominant change was shrinkage of the neurons, which in Nissl preparations stained a deep blue. The glia remained inactive. The basal ganglia, cortex, cerebellum and meninges were normal.

CASE 3.—S. Z., a girl aged 19 years, had coryza and a cough, followed by pain in the back, numbness and progressive weakness of all the extremities eight days before her admission to the hospital.

Examination.—There were bilateral facial paralysis of peripheral type, mild paresis of the uvula and tongue, mild dyspnea, dysarthria, dysphagia and flaccid tetraplegia, with absence of all deep and superficial reflexes. The paralysis was complete in the lower extremities and nearly complete in the upper extremities, where it was without definite proximal or distal predilection. There was moderate paresis of the deep spinal, the abdominal and the accessory respiratory muscles, but the function of the diaphragm was normal. Vibratory sensation was absent at the ankles and wrists; the sense of position was absent in the toes and impaired in the fingers, and there was distal blunting of all modalities of superficial sensation to the midthigh in the lower extremities and to the elbows in the upper extremities. All active and passive movements were painful, and there were severe generalized tenderness of the muscles and mild nuchal rigidity. The optic disks, the reactions of the pupils, the extraocular movements and the function of the muscles of mastication and of the sphincters were normal.

Laboratory Examination.—The Kahn reaction of the blood was negative, and urinalysis showed nothing abnormal. There were 14,800 white blood cells per cubic millimeter, of which 81 per cent were polymorphonuclear leukocytes. The cerebrospinal fluid was clear and faintly xanthochromic and contained 5 lymphocytes per cubic millimeter; it was under a pressure of 60 mm. of water, and there was no manometric block. The Kahn reaction of the cerebrospinal fluid was negative; the colloidal gold curve was 1144433221; the Pandy and Nonne-Apelt reactions were positive, and the total protein content was 1,333 mg. per hundred cubic centimeters. A pellicle formed on the fluid's standing. Cultures of the spinal fluid yielded no growth, and attempts to isolate a virus by chick embryo culture and intracerebral inoculation of mice were unsuccessful.

Course in the Hospital.—Ten days after admission increasing paralysis of the respiratory muscles required the use of a Drinker respirator, in which the respirations improved temporarily. On the sixteenth day of illness pneumonia developed, and the patient died three days later. The temperature was normal until the onset of pneumonia; the pulse and respiratory rates were continuously elevated, the rates varying with the degree of respiratory distress. The duration of the disease was twenty-one days.

Pathoanatomic Examination. — Peripheral Nerves: The axis-cylinders were greatly swollen, appearing six

or eight times as thick as normal, and seemed to compress remnants of degenerated myelin. The latter was broken down into small fragments, which filled the perineural sheaths in a disorderly manner; the Schwann cells were proliferated, and their nuclei were swollen; there were occasional gitter cells; the perineural tissue was moderately increased.

Posterior Root Ganglia: The neurons showed advanced axonal degeneration and were greatly swollen; their tigroid substance was destroyed, and the nuclei were shrunken or no longer visible.

Central Nervous System: There was advanced axonal degeneration in the lumbosacral segments, while in the thoracic and cervical segments the neurons were shrunken, staining a homogeneous deep blue. In the midbrain, the basal ganglia and the cortex of both hemispheres the neurons stained pale blue, the tigroid substance appearing dustlike, or not being visible at all. Marchi preparations showed numerous myelin fragments in the white matter of the thoracic, lumbar and sacral segments of the spinal cord. Unfortunately, no Marchi preparations were available from segments above the upper thoracic level. The meninges and cerebellum appeared normal.

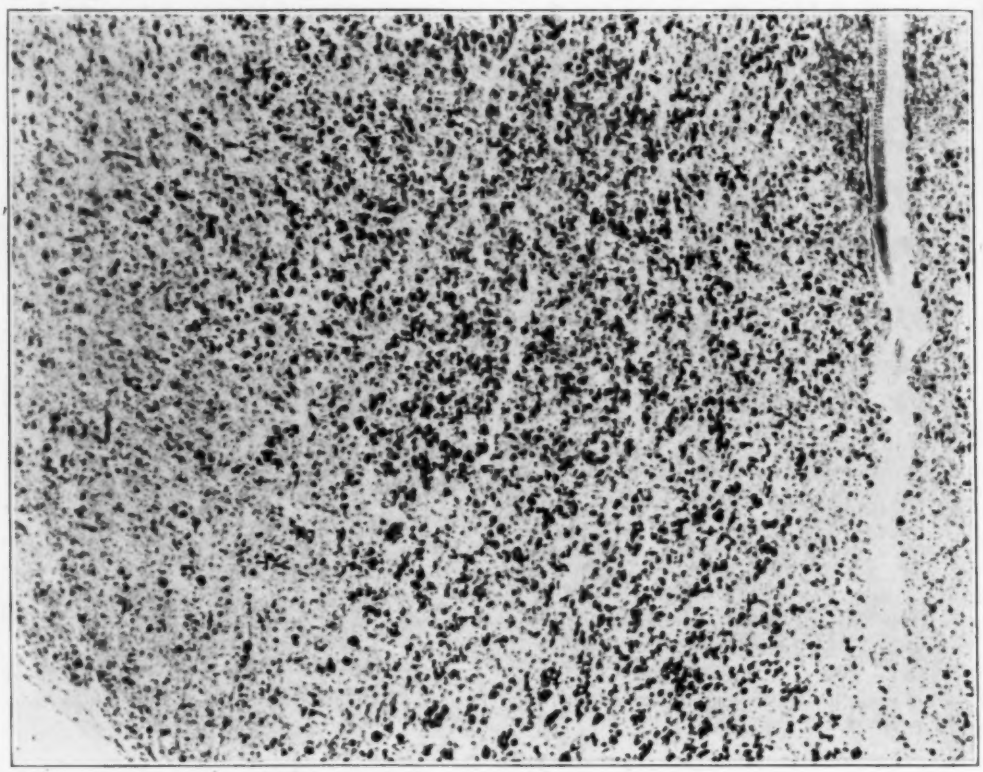

Fig. 3.—Fasciculus gracilis and fasciculus cuneatus with numerous degenerated myelin fragments (upper lumbar cord). Marchi method; Zeiss planar lens, 20 mm.

COMMENT

Although it is the consensus that in the Guillain-Barré syndrome [1] the peripheral nerves regularly undergo severe degeneration, little is known of the pathoanatomic changes in the central nervous system. Most authors reported either no changes at all or alterations of a mild or reversible nature. Only in 3 cases has definite degeneration been observed. In these cases the clinical course was protracted (seven and a half, ten and nineteen months respectively), and the degeneration was restricted to the posterior columns of the spinal cord (Russell and Moore [4]; Gilpin, Moersch and Kernohan [5]) and the dorsal spinocerebellar tracts (Shaskan, Teitelbaum and Stevenson [6]).

As our observations show, the central nervous system may undergo extensive and fatal damage to its myelin and parenchymal cells in the early acute stages of the disease; these changes are degenerative and stimulate only a limited cellular response. Even in the peripheral nerves, which possess a powerful regenerative capacity, the cellular activity remains restricted to moderate

4. Russell, W. D., and Moore, W. L.: Permanent Damage to the Nervous System Following an Attack of Polyradiculoneuritis (Guillain-Barré Syndrome), Arch. Neurol. & Psychiat. **49**:895 (June) 1943.

5. Gilpin, S. F.; Moersch, F. P., and Kernohan, J. W.: Polyneuritis: A Clinical and Pathologic Study of a Special Group of Cases Frequently Referred to as Instances of Neuronitis, Arch. Neurol. & Psychiat. **35**: 937 (May) 1936.

6. Shaskan, D.; Teitelbaum, H. A., and Stevenson, L. D.: Myeloradiculoneuronitis with Cell-Protein Dissociation, Arch. Neurol. & Psychiat. **44**:599 (Sept.) 1940.

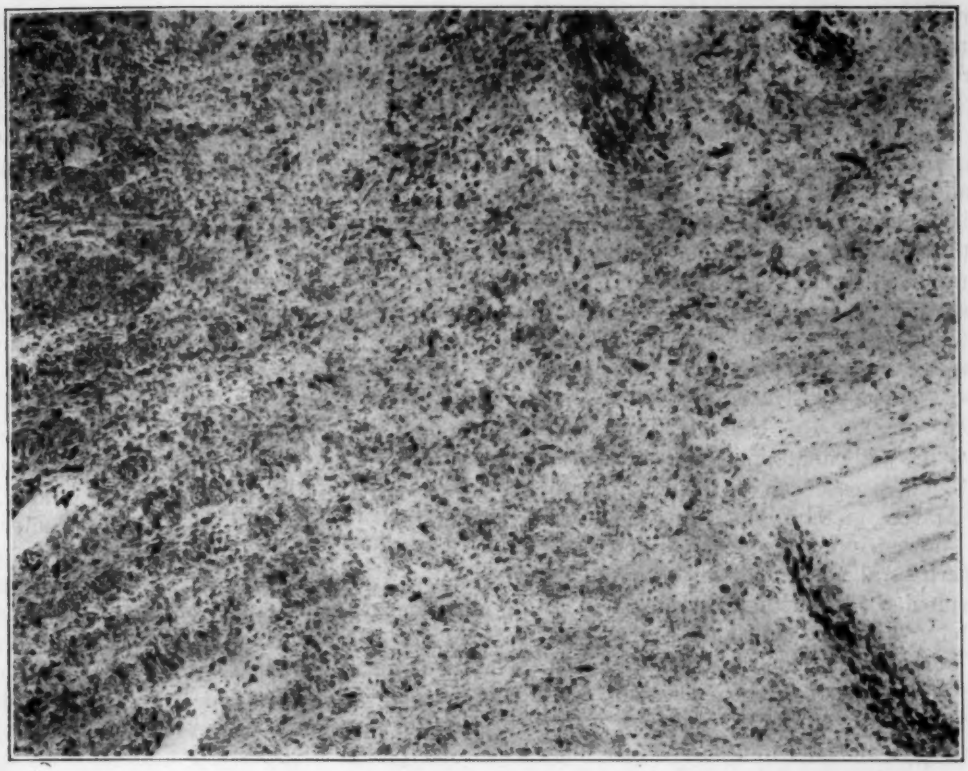

Fig. 4.—Section through the medulla at the level of the twelfth nerve, showing advanced degeneration of the myelin in the medial lemniscus, the fibers of the hypoglossus nerve and the reticular substance. Marchi method; Zeiss planar lens, 20 mm.

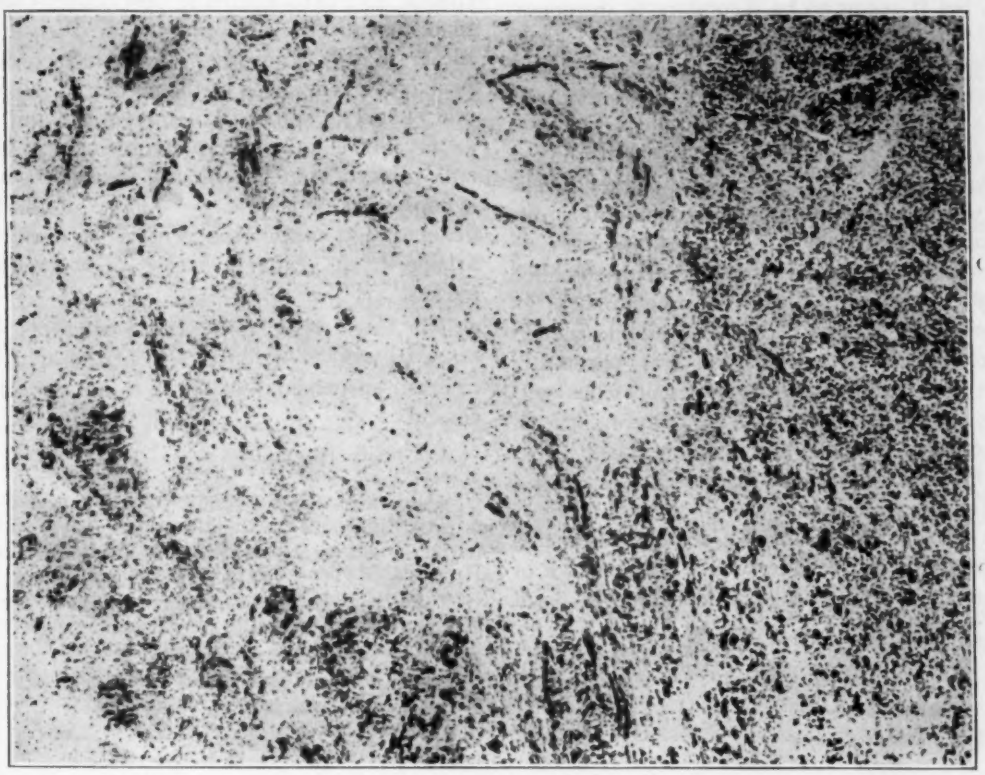

Fig. 5.—Posterior horn and fasciculus gracilis and fasciculus cuneatus laden with numerous myelin fragments (lumbar portion of cord). Marchi method; Zeiss planar lens, 20 mm.

proliferation of the Schwann elements and of the perineural connective tissue. This lack of cellular reaction is even more striking in the central nervous system, where the regenerative power is negligible, a condition which accounts for the frequently reported failure of cellular preparations to demonstrate definite changes. The histologic analysis is rendered still more difficult by lack of demonstrable signs of lipid degeneration in scarlet red and Weigert preparations, which in cases of this disorder give positive results only with the chronic form. In all 3 of our cases of the acute form both these methods failed to yield conclusive results.

In our opinion the character and the full extent of the pathoanatomic changes in the acute stage of the disease can be demonstrated only by the Marchi method, since in our cases this technic showed extensive degeneration not only in the peripheral nerves but in the white matter of the spinal cord and of the brain stem. Unfortunately, we were not able to employ this technic at levels higher than the midbrain, so that the full extent of the degeneration remained unknown. We were able, however, to trace it through the medial lemniscus, which suggests that the morbid process reached at least the level of the thalamus.

Degeneration of the parenchyma occurs regularly, but it seems to be secondary to degeneration of the myelin and its extent varies. Three histologic types may be distinguished. The most conspicuous type is that of axonal degeneration: It was regularly seen in the posterior root ganglia and in the lumbosacral segments of the cord, but occurred in few cells at higher levels. This type of degeneration has considerable differential value. It was noted by Spielmeyer [7] in cases of polyneuritis associated with so-called Landry's paralysis. This we can confirm: In 7 cases of the latter syndrome available in this laboratory axonal degeneration was constantly present in the lumbar segments, its presence suggesting a possible pathoanatomic relation, at least in some cases, between the Guillain-Barré [1] syndrome and the disturbance diagnosed as Landry's paralysis.

Less conspicuous than the axonal degeneration, but much more widespread, is shrinkage of the neurons, which stained a deep blue in Nissl preparations. These cells could be seen throughout the spinal cord and the brain stem. This type apparently represents a degenerative phase preceding axonal degeneration, since both processes were frequently present in the same nucleus.

The third type of parenchymal degeneration was noted in case 3, in which the neurons stained poorly and appeared pale. This change was universal, affecting also the basal ganglia and the cortex of both hemispheres. It is possibly toxic. Its true nature and significance remain obscure, but its severity corresponded to the stormy clinical course.

Little is known of the involvement of the autonomic nervous system. Clinical manifestations in some cases indicate a possible implication early in the course of the disease. Abdominal symptoms without a demonstrable anatomic basis were present in the case of Russell and Moore [4] and in our case 1. Pathoanatomic changes were reported by Roseman and Aring,[8] who noted degenerative changes in the sympathetic ganglia, and by Paliard and Dechaume,[9] who observed lymphocytic infiltration and an increased number of satellite cells in the solar plexus.

SUMMARY

It may be stated that the uniformity of the clinical and pathoanatomic observations suggests that the disorder represents a disease entity rather than a syndrome. It is characterized by primary degeneration of the myelin in the peripheral nerves, spinal ganglia, cord and brain stem. The equally severe involvement of efferent and afferent pathways and the disregard for synapses exclude the possibility of secondary degeneration within the central nervous system arising from primary disease of the peripheral nerves.

The cause remains obscure; attempts in our cases to recover a "virus" from the spinal fluid or from suspensions of nerve tissue were unsuccessful.

University Hospital.

7. Spielmeyer, W.: Histopathologie des Nervensystems, Berlin, Julius Springer, 1922, p. 268.

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9. Paliard, F., and Dechaume, J.: Forme périphérique de l'encéphalite épidémique an polynévrite infectieuse primitive, Lyon méd. **148**:173 (Aug. 16) 1931.

LESIONS IN THE BRAIN ASSOCIATED WITH MALARIA

PATHOLOGIC STUDY ON MAN AND ON EXPERIMENTAL ANIMALS

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Pathologic changes in the brain frequently are noted in patients who have died of malaria. Petechiae in the meninges and the brain tissue are probably the lesions most often observed. Gaskell and Millar [1] stated that these hemorrhages resulted primarily from degeneration of the endothelial cells lining the capillaries. Other investigators have expressed the opinion that red blood cells accumulate along the injured capillary walls and hinder the exchange of nutritive materials.[2] Occlusion of the cerebral capillaries by thrombi composed of parasitized erythrocytes is considered usually to be the basis for the development of the hemorrhages. Laveran [3] was one of the first to claim that these hemorrhages developed from thrombi.

Cellular reactions within the brain substance and in the meninges also have been described in cases of malaria.[4] Malarial nodules have been observed in the subcortical areas of the cerebrum and infrequently in the cerebellum.[4] Margulis [5] apparently was one of the first to describe this lesion. He suggested that it resulted from stasis and thrombosis of the neighboring capillaries since it was frequently associated with hemorrhages. Dürck [6] described a similar lesion unassociated with hemorrhages and expressed the opinion that it developed as the result of the action of malarial toxin on the capillaries and on the brain tissue. These granulomatous nodules in the brain are usually referred to in the literature as "Dürck granulomas." Both Dürck [6] and Thomson and Annecke [4] discussed the pathogenesis of this lesion.

Degenerative lesions in the cells of the brain were described by Marchiafava and Bignani [7] as early as 1890. They reported the presence of chromatolysis in large nerve cells, accompanied by other degenerative changes. Lafora [8] also described chromatolysis, swelling and vacuolation of the cytoplasm, loss of Nissl granules and degeneration of the medullated fibers in the brain of patients who died of the malignant types of malaria.

A variety of clinical manifestations have been observed in patients with acute and chronic malaria.[9] De Vries [10] reported a case of cerebellar ataxia with hyperactive tendon reflexes, tremor, slurring speech and nonconvergence of the eyes. Simpson and Sagehiel [9c] reported a case of malaria in which there were manifestations of a cerebellar syndrome, with weakness, ataxia and dysmetria of the extremities. Cerletti [11] emphasized the frequence with which

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3. Laveran, A.: Traité des fièvres palustres, Paris, O. Doin, 1884, pp. 482-483; cited by Mannaberg.[2]

4. Thomson, J. G., and Annecke, S.: Observations on the Pathology of the Central Nervous System in Malignant Tertian Malaria, with Remarks on Certain Clinical Phenomena, J. Trop. Med. **29**:343-346, 1926.

5. Margulis, M. S.: Zur Frage der pathologisch-anatomische Veränderungen in Gehirn bei bosärtiger Malaria, Neurol. Centralbl. **33**:1019-1024, 1914.

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7. Marchiafava, E., and Bignani, A.: On Summer-Autumn Malarial Fever, London, The New Sydenham Society, 1894.

8. Lafora, G. R.: On the Changes of the Nervous System in Pernicious Malaria and the Neurological Sequelae Resulting from Malarial Toxemia, J. f. Psychol. u. Neurol. **19**:209-220, 1912.

9. Masson, C. B.: Effects of Malaria on the Nervous System with Special Reference to Malarial Psychoses, Am. J. M. Sc. **168**:334-371, 1924. (*b*) Turner, C. C.: The Neurologic and Psychiatric Manifestations of Malaria, South. M. J. **29**:578-586, 1936. (*c*) Simpson, W. M., and Sagehiel, J. L.: Cerebral Malaria, U. S. Nav. M. Bull. **41**:1596-1602, 1943.

10. de Vries, E.: Nervous Complications in Pernicious Malaria, China M. J. **41**:503-508, 1927.

11. Cerletti, U., 1909, cited by Thomson and Annecke.[4]

a cerebellar syndrome occurred in cases of malaria. Deaderick,[12] however, expressed the opinion that symptoms originating from the cerebellum were present only in rare instances. Neurologic lesions have been observed infrequently in experimental animals. Simpson,[13] in June 1944, described them in a turkey infected with Plasmodium durae. He stated:

This animal seemed to be partially paralyzed for several hours before its death, and although it was able to flap its wings, it could not raise its head or stand on its legs.

METHODS AND MATERIAL

The material used in this study consisted of the brain of a child who died in the acute stage of infection with Plasmodium falciparum, the brains of 3 monkeys infected with Plasmodium knowlesi and the brains of a series of ducks and chicks infected with Plasmodium lophurae.

The human brain was removed within three hours after death. Two of the monkeys were perfused with a 10 per cent concentration of solution of formaldehyde U. S. P. immediately after they were bled to death.

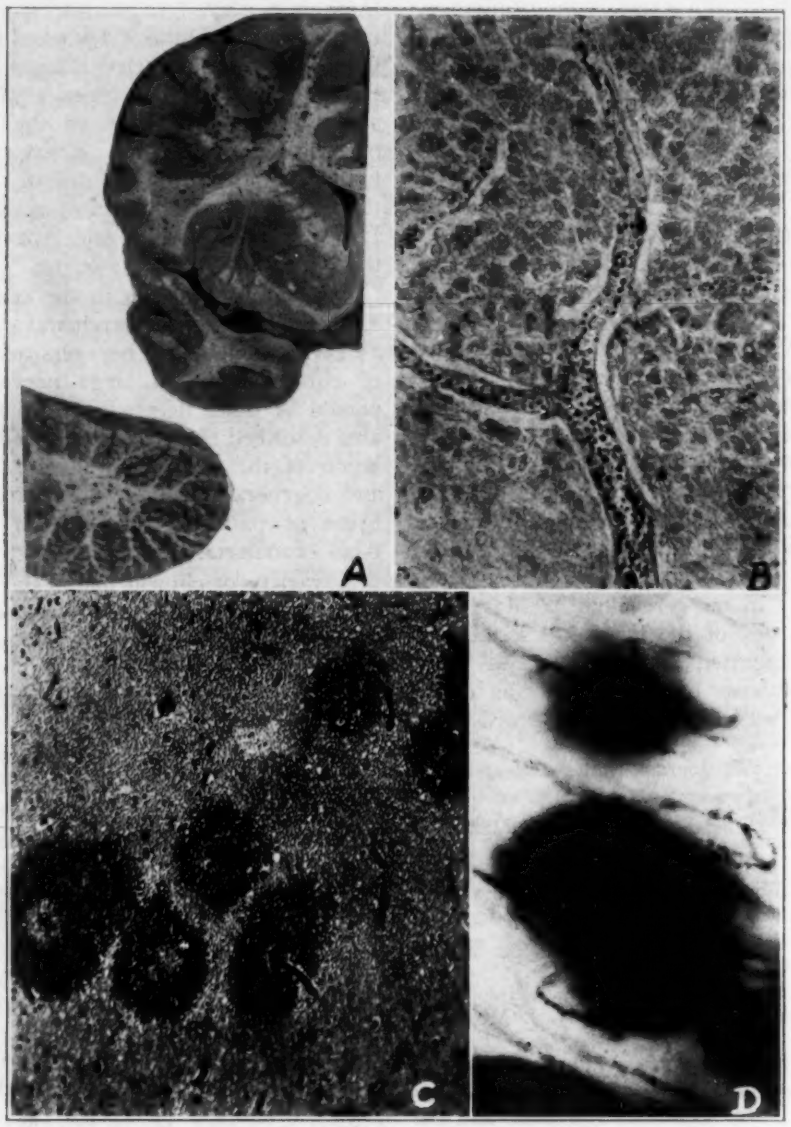

Fig. 1.—Petechiae in the brain of a child aged 7 years who died of infection with P. falciparum. *A*, petechiae in the cerebral hemisphere and cerebellum. *B*, parasitized erythrocytes filling the lumen of a blood vessel. A hemorrhage has occurred around this vessel. Hematoxylin and eosin; × 430. *C*, petechiae associated with capillaries. The red cells may form the ring type of hemorrhage. Hematoxylin and eosin; × 100. *D*, capillaries throughout the brain filled with parasitized cells. The petechiae here appear as black areas. Tissue cleared in alcohol, benzine and methyl salicylate; × 100.

12. Deaderick, W. H.: A Practical Study of Malaria, Philadelphia, W. B. Saunders Company, 1909.

13. Simpson, M. L.: Exoerythrocytic Stages of Plasmodium Durae, J. Parasitol. **30**:177-178, 1944.

The brain from the third monkey was obtained within thirty minutes after death by bleeding. The brains from the ducks and chicks were removed at varying intervals after the intravenous injection of P. lophurae. A cervical clamp was applied, and the brain was removed and placed in the fixative within one minute.

The following fixatives were used: a 10 per cent concentration of solution of formaldehyde U. S. P., 95 per cent alcohol; Zenker's fluid, and Bouin's solution. Paraffin sections and the following staining technics were used: hematoxylin and eosin, 0.5 per cent thionin, Weil's iron hematoxylin stain for myelin sheaths, osmic acid and scarlet R for fat and Bodian's and Bielschowsky's silver technics.

The ducks used in this study usually had a high degree of parasitemia such that approximately 90 per cent died during the early stage of the infection. Of the remaining 10 per cent, all manifested clinical neurologic signs within two to eight weeks. In this study we used only brains of birds that were killed at varying intervals during the course of the disease.

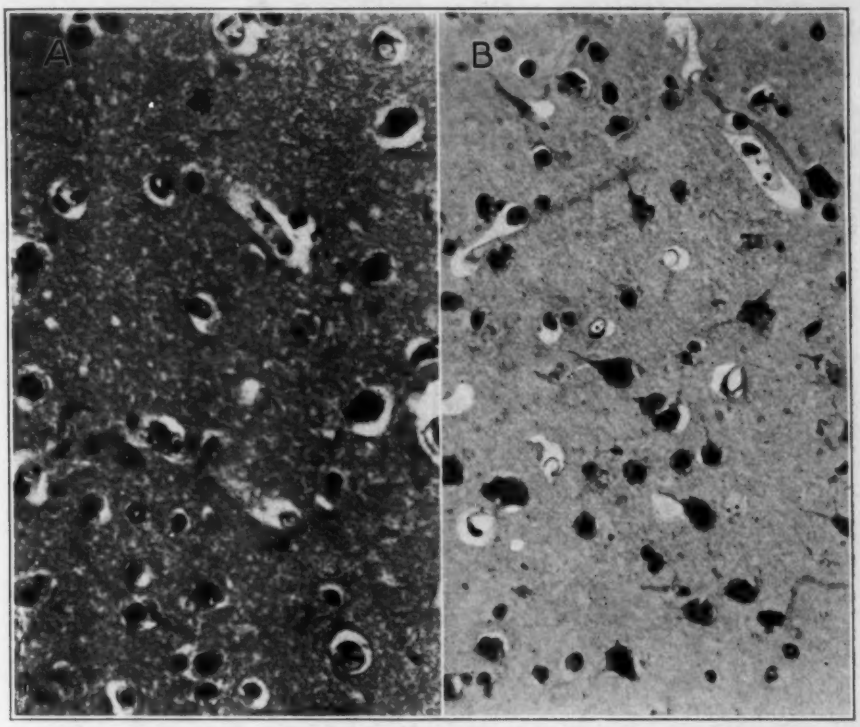

Fig. 2.—*A*, section of the cerebral cortex of the same brain from which sections in figure 1 were taken, showing enlarged perivascular and pericellular spaces resulting from capillary permeability. In our opinion, these changes are too pronounced to be artefacts. Hematoxylin and eosin; × 430. *B*, cells showing various degenerative changes. Thionin stain; × 430.

OBSERVATIONS

Human Brain.—The child, aged 7, was admitted to the hospital with the chief complaint of abdominal pain.[14] Approximately forty hours after admission she was comatose. Malarial parasites were demonstrated in the peripheral blood only four hours preceding death. At this time the total red blood cell count was 1,060,000, the hemoglobin concentration 5 Gm. and the white blood cell count 22,200 per cubic millimeter. Fifteen per cent of these red blood cells were parasitized. Approximately one half of these cells contained from 2 to 4 parasites. The carbon dioxide–combining power was 26 volumes per cent. Autopsy was performed approximately three hours after death.

The convolutions of the brain were slightly swollen. Petechiae were numerous both in the meninges and on the cut section of the cerebrum and cerebellum (fig. 1). These hemorrhages occurred in both the gray and the white matter of the brain; however, they were more numerous in the latter area. The blood vessels in the cerebral cortex were notably congested with parasitized erythrocytes. The endothelial cells lining the vessels were swollen; a few contained granules of pigment and fat, while others were either free in the lumen or partially attached to the vessel wall. The perivascular and pericellular spaces were greatly enlarged, giving to the tissues a cribriform appearance (fig. 2*A*). Occasionally these spaces were surrounded by a necrotic area.

All the nerve cells in the gray matter of the cerebral cortex appeared to show pathologic changes (fig. 2*B*). This lesion varied from only a change in the staining reaction to disintegration of the cell. Many nerve cells showed complete exhaustion of the Nissl material. Some of the cells presented sclerotic changes, with pyknotic nuclei, shrunken cytoplasm and tortuous processes. A few cells exhibited pigmentary degeneration, with varying quantities of yellow-brown granules clustered about the nucleus. This pigment usually was more pronounced at the apical poles of the cells. Numerous cells showed acute swelling and vacuolar disintegration. These pathologic changes exhibited neither regional

14. Rigdon, R. H.: A Consideration of the Mechanism of Death in Acute Plasmodium Falciparum Infection: Report of a Case, Am. J. Hyg. **36**:269-275, 1942.

specificity nor uniformity within any given area. The remaining portions of the brain and spinal cord presented similar cell changes. The lesions decreased in severity from the cerebral cortex to the spinal cord. In the latter region altered staining reactions, chromatolysis and hyalinization of the cytoplasm were the changes observed.

The white matter of the brain and spinal cord presented the most spectacular lesions, in contrast to the less conspicuous lesions of the gray substance. In histologic sections of the cerebral hemispheres, the subcortical white matter, the corona radiata and the internal capsule were literally strewn with holes, varying in size from 1.5 to 80 microns in diameter (fig. 3 *B*). The glia and nerve fibers were compact and swollen and were stained more deeply around the margin of these spaces than in the surrounding tissue. Fragments of degenerating fibers might be seen either free or extending across some of the spaces. In this paper we refer to these spaces as "perforate lesions."

These "perforate lesions" were present also in the substantia alba of the cerebellum and in the fiber pathways of the brain stem and the spinal cord. They were fewer, however, than in the cerebral hemisphere. They occurred infrequently in the gray matter.

Another type of lesion observed in the brain was an irregular, oval necrotic area, varying in size from 50 by 100 to 500 by 700 microns (fig. 4 *A*). These foci appeared as light-staining, finely reticulated areas with a dark-staining center. Glial fibers and fragmented demyelinated nerve fibers constituted the lighter-staining tissue, while glia cells, large mononuclear cells, malarial pigment and tissue debris made up the darker center. The number of glia cells varied; many showed amitotic division. Small blood vessels, either intact or fragmented, were present within the necrotic areas. Red blood cells, both parasitized and nonparasitized, were present in varying numbers within these lesions. In some areas the red blood cells were intact; in others they were hemolyzed, while a few showed only fragmented erythrocytes. Large mononuclear cells were also present within these necrotic foci. They had large, open, pale-staining nuclei and prominent nucleoli. Some showed phagocytosed particles within their cytoplasm. These phagocytic cells were sometimes attached to the wall of the fragmented vessels.

Other areas of necrosis, similar to the granulomatous lesions previously described, appeared as irregular, pale-staining patches, varying widely in both size and shape. These gave to the tissue a lacelike appearance. The

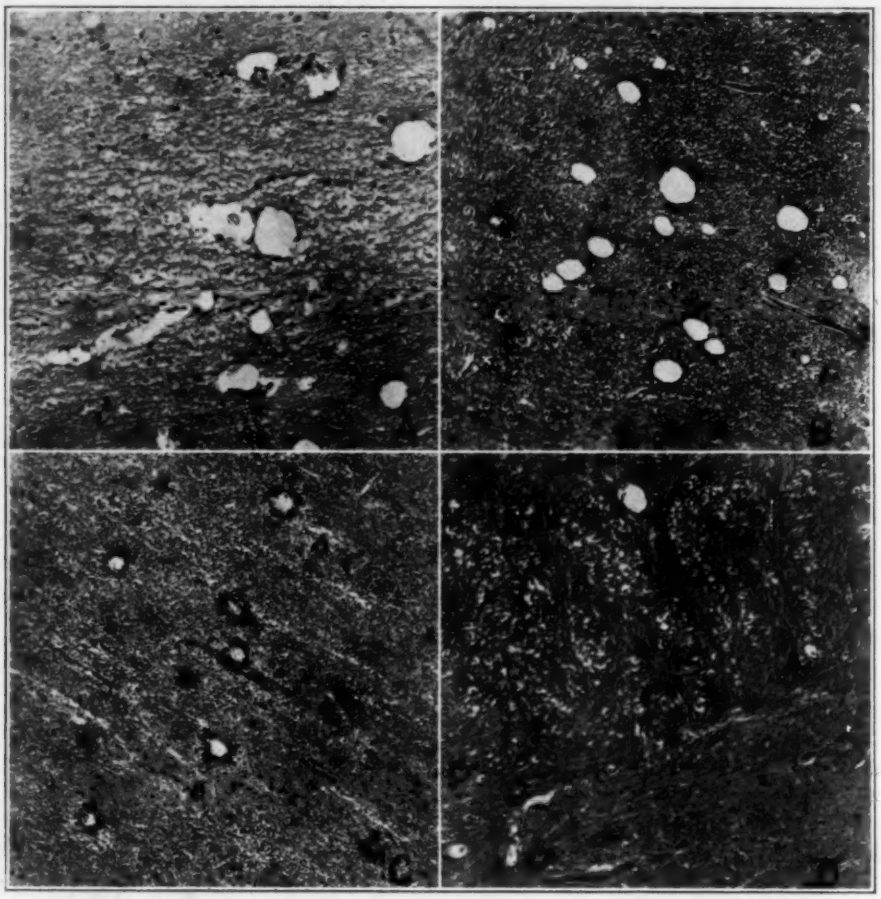

Fig. 3.—Sections from the same brain as that which appears in figures 1 and 2. *A*, areas of necrosis in the corona radiata, with a "lacelike" appearance; *B*, numerous circumscribed spaces referred to in the text as "perforate lesions," varying in size from 1.5 to 80 microns. These lesions gave a cribriform appearance to the internal capsule and the corona radiata of this brain. Similar lesions occurred in the brains of the monkeys, ducks and chicks which were similarly infected. *C*, subcortical white matter of the monkey brain, showing "perforate lesions," preceded by an early degenerative lesion in the myelin, as indicated by variations in staining. *D*, section of the midbrain of the same monkey, showing a picture similar to that in *C*.

number of glia cells was decreased in these areas (fig. 3*A*).

Focal areas of myelin degeneration 25 to 50 microns in diameter were demonstrated in thick histologic sections. These stained uniformly gray-blue with Weil's technic, light red with thionin and orange-pink with hematoxylin and eosin. The periphery of these lesions stained more deeply than the center (fig. 3*B*).

Necrotic lesions like those described in the white matter of the cerebrum occurred in the cerebellum, but less frequently. They were more numerous in the molecular layer of the cerebellar cortex than in the substantia alba.

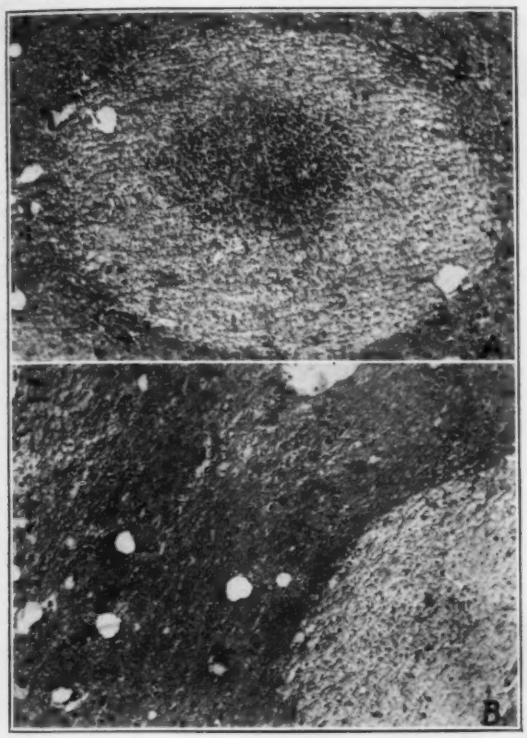

Fig. 4.—Lesions in the white matter of a brain of a child who died of infection with P. falciparum. *A*, "Dürck granulomas," showing extensive glial proliferation; *B*, granulomas, "perforate lesions" and "lacelike" necrosis in the corona radiata. Hematoxylin and eosin; × 100.

The Purkinje cells were greatly reduced in number (fig. 5*A*). Some of these cells which remained showed acute swelling with chromatolysis; others were sclerotic with tortuous processes, and a few contained granules of yellow-brown pigment about the nucleus. No demonstrable changes were present in the granule, basket and Golgi cells.

Monkey Brain.—The data, as shown in the accompanying table, were obtained from the 3 monkeys used in this study. The brains did not show any significant macroscopic changes. The blood vessels in the brain of monkey 3, which was not perfused, were filled with parasitized cells similar to the vessels in the child's brain. The perivascular and pericellular spaces were enlarged in each of the 3 brains. The cytologic changes were similar in the monkey's brain to those in the child's brain. Focal areas of demyelination were also present. They occurred in both the gray and the white matter throughout the brain and the spinal cord of the 3 monkeys (fig. 3*C* and *D*). They were more numerous in the cerebrum than in the spinal cord and occurred more frequently in the white than in the gray matter. The "perforate lesion" and the areas of "lacy degeneration" also were present, but were less conspicuous in the monkey brain than in the human brain.

The pathologic changes in the cerebellum were similar to those in the cerebrum. The Purkinje cells were notably depleted (fig. 5*B*). The remaining Purkinje cells showed chromatolysis and other types of degeneration. The granule, basket and Golgi cells appeared normal.

Duck Brain.—No gross lesions were observed in the brains of the ducks. However, microscopic lesions were present, and basically they were similar to the lesions

Laboratory Data on Monkeys Infected with Plasmodium Knowlesi

Monkey	Experimental Day	Time	Red Blood Cells, Millions	Percentage of Red Cells Parasitized
1	3	9:30 a.m.	3.15	0.4
	4	9:00 a.m.	3.1	4.5
	5	9:00 a.m.	3.15	4.5
	5	2:30 p.m.	....	4.8
	6	9:00 a.m.	1.9	42.6
	6	2:00 p.m.	1.95	46.8
	7	10:00 a.m.	Killed by bleeding	
2	2	.....	....	6.6
	3	.....	....	39.6
	3	.....	Killed by bleeding	
3	2	.....	....	6.3
	3	.....	....	51.7
	3	.....	Killed by bleeding	

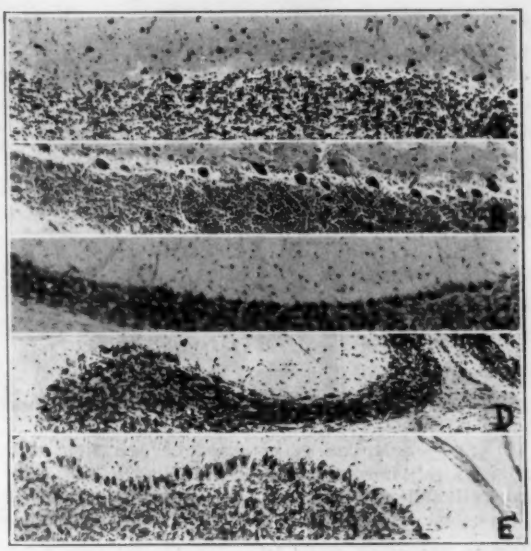

Fig. 5.—Depletion of Purkinje cells of the cerebellum, with varying degrees of degeneration of the remaining cells in a child and in experimental animals infected with malaria. *A* is from the child's brain; *B*, from the monkey brain; *C*, from the duck brain, and *D*, from the chick brain. *E* is a section from the cerebellum of a normal chick, shown for comparison. Thionin stain; × 100.

in both the human and the monkey brain. The changes that occurred in the Purkinje cells in the duck brain during the course of malaria may be considered under the following stages: (1) the normal, or resting stage;

(2) the stage of sclerosis; (3) the stage of edema, showing both early and late phases; (4) the stage of exhaustion and (5) the stage of disintegration.

The normal resting Purkinje cell in the duck brain tended to be pyriform, like Purkinje cells in other animals. The cytoplasm was filled with large, uniformly distributed Nissl flakes. The nucleus, which was oval to spheroid, was centrally placed and filled with acidophilic chromatin material. These granules were distributed over a linin net, dispersed around the inner margin of the nuclear membrane and concentrated about a prominent, centrally placed nucleolus, which consisted of two or three circular bodies. With hematoxylin and eosin the cytoplasm of the normal resting cell stained pale blue and the nuclear structure darker blue. The staining properties were such that the cell was poorly delineated from the surrounding tissue (fig. 6 *A*).

In the second stage the sclerotic cell was shrunken, triangular to spindle shaped and filled with Nissl material. The nucleus was pyknotic, eccentric and obscured by the deeply stained cytoplasm. The dendritic processes of many of these cells were tortuous (fig. 6 *B*).

The edematous cell in the early phase was approximately twice the size of a normal resting cell. The tigroid substance was depleted except at the periphery, where it appeared in large bodies. The chromatin granules of the nucleus were compressed into a centrally placed, deeply staining mass, surrounded by an edematous area, which stained either clear or cloudy (fig. 6 *C*). Figure 6 *D* showed the late phase of the edematous cell, in which the edema had decreased. The chromatin granules were scattered throughout the nucleus, and the Nissl bodies were piled up about the nucleus and located at the periphery of the cell. The cytoplasm stained a muddy pink with hematoxylin and eosin.

The cell in the exhausted stage appeared as a homogeneous, pale pink–staining mass of protoplasm, with ill defined nucleus and fuzzy outline. The Nissl substance and nuclear chromatin were completely absent. Some of these cells showed vacuolar degeneration and disintegration (fig. 6 *E*).

The number of Purkinje cells in a transverse section of a folium varied in the ducks with malaria as compared with the number in normal ducks. It is of interest to observe that the number of Purkinje cells was least in the ducks which survived the acute stages of the malarial infection and subsequently had neurologic manifestations (fig. 5 *C*). The remaining Purkinje cells showed the various stages of activity and degeneration, as previously described.

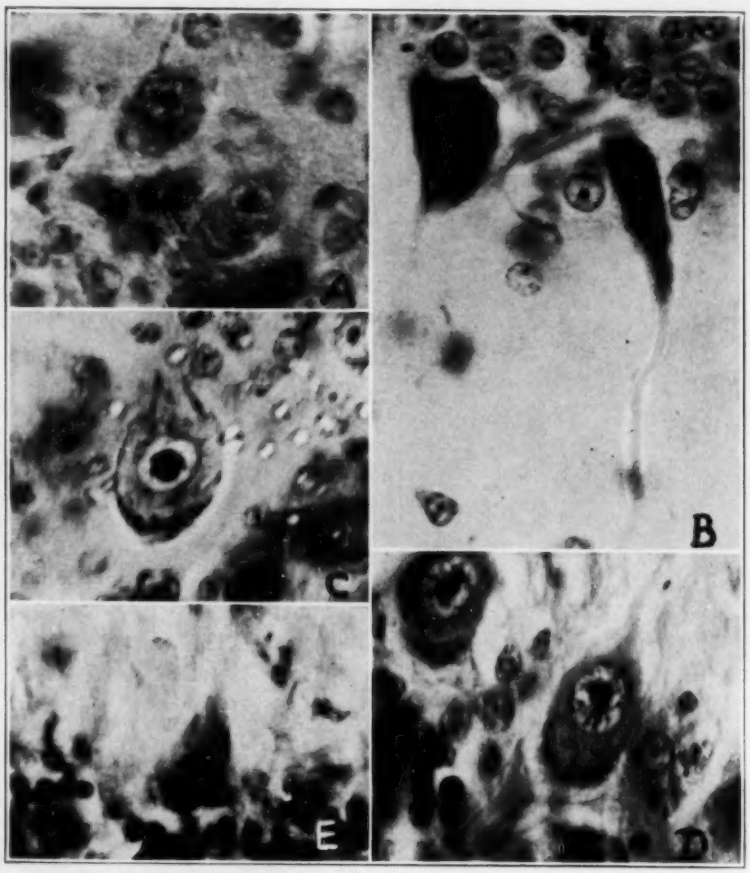

Fig. 6.—Stages of activity and degeneration of Purkinje cells from the cerebellum of a duck infected with malaria. *A*, normal resting cell; *B*, pyknotic cell; *C*, early phase of edematous cell; *D*, late stage of edematous cell, and *E*, exhausted cell. Hematoxylin and eosin; × 910.

The cells in the nuclei of the cerebellum showed pathologic changes similar to those in the Purkinje cells. Acute swelling and vacuolar degeneration occurred in these nuclear cells in the moribund bird (fig. 7).

Chick Brain.—The pathologic changes in the cerebellum of the chick were similar to those in the duck. The depletion of the Purkinje cells in a chick with

malaria is shown in figure 5 *D*. This may be compared with the condition in the brain of the normal chick (fig. 5 *E*).

COMMENT

The lesions which we have described in the brain and spinal cord in association with malaria were fundamentally and basically the same in the child, monkey, duck and chick.

Edema was a constant feature. It could be detected even grossly. In histologic section it appeared as a notable enlargement of the perivascular and pericellular spaces. We are cognizant of the fact that a similar process may occur as a technical artefact. However, we consider it too pronounced for an artefact and believe that it is the earliest lesion associated with malaria.

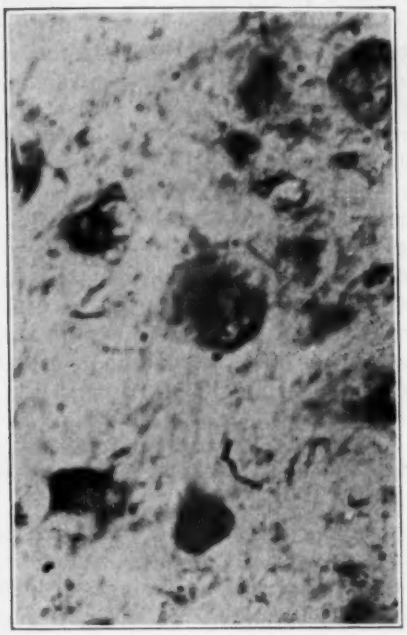

Fig. 7.—Cells in the cerebellar nuclei of a duck with a severe malarial infection, showing vacuolar degeneration. Thionin stain; × 430.

The nerve cells in the cerebral cortex of the child were more severely damaged than those in the monkey. These cytologic changes were less pronounced in the more caudal regions of the brain. This variation in the human and in the monkey brain may have been influenced by the degree of parasitemia, the length of the infection and the susceptibility of the brain to injury.

The Purkinje cells of the cerebellum were depleted in the human, monkey, duck and chick brains. The progressive changes which precede this depletion were followed in the duck and chick brains. We recognize that all these cell changes were not pathologic. The earlier ones may represent normal physiologic activity of the cell in response to some stimulus in malaria. The later changes were irreversible and led to death of the cell. These changes in the Purkinje cells are not specific for malaria. Similar ones have been described in cases of fatigue and exhaustion,[15] shock,[16] anemia [17] and many other conditions.[18]

In the literature which we have reviewed three specific lesions have been described, namely petechiae,[1] malarial nodules [4] and the Dürck granulomas.[6] Each of these lesions has been observed in our studies; in addition, we have noted other degenerative changes in the myelin, the earliest manifestation of which was a variation in staining. Later the myelin might be partially or completely removed, leaving either perforations or focal areas of demyelination with a "lacelike" appearance. Petechiae were present in the child's brain; they occurred only in the focal areas that we have referred to as granulomas. It is of interest to observe that red blood cells were not present in all the areas of necrosis. This observation suggests that the hemorrhages were secondary to the necroses. Why should red blood cells occur in one area of necrosis and not in another?

It appears more reasonable that the answer lies in the vascular supply about the necrotic area. In the focal areas of necrosis the circulation is maintained. In contrast, in the diffuse, "lacelike" areas of degeneration the blood flow has ceased. In such areas, purely by chance, a greater number of parasitized red blood cells accumulate within the lumens, thereby obstructing the circulation. Inasmuch as the blood flow has ceased, it is obvious that hemorrhage cannot occur. This process has been interpreted as thrombosis. In our opinion it is only the end result of stasis.

It is easy to understand how one would conclude from seeing histologic sections of the brain in cases of infection with P. falciparum that the

15. Hodge, C. F.: A Microscopical Study of Changes Due to Functional Activity in Nerve Cells, J. Morphol. **7**:95-168, 1892. Dolley, D. H.: The Neurocytological Reaction in Muscular Exertion: I. Preliminary Communication; the Sequence of the Immediate Changes in the Purkinje Cells, Am. J. Physiol. **25**:151-171, 1909-1910.

16. Dolley, D. H., and Crile, G. W.: The Pathological Cytology of Surgical Shock: I. Preliminary Communication; the Alterations Occurring in the Purkinje Cells of the Dog's Cerebellum, J. M. Research **20**:275-295, 1909.

17. Dolley, D. H.: The Morphological Changes in Nerve Cells Resulting from Overwork in Relation with Experimental Anemia and Shock, J. M. Research **21**:95-113, 1909.

18. (*a*) Courville, C. B.: Untoward Effects of Nitrous Oxide Anesthesia, Mountain View, Calif., Pacific Press Pub. Assoc., 1939, p. 150. (*b*) Hartman, F. W.: Some Etiological Factors and Lesions in Cerebral Anoxia, Am. J. Clin. Path. **8**:629-648, 1938.

capillaries are occluded either by thrombi or by emboli. However, as far as we have been able to determine from a review of the literature, no one has observed the progressive development of a thrombus on the walls of the vessels in the brain in a case of malaria. Furthermore, in our study we have not observed such a process. The presence of a sufficient number of parasitized red blood cells to fill the lumen of capillaries should not be interpreted necessarily as an embolus. Masses of parasitized red blood cells have been demonstrated only infrequently in the peripheral blood of patients with malaria.[19] If emboli are characteristic of malaria, it would seem that the evidence from the numerous studies already made on this disease should be conclusive. The demonstration of a variety of pathologic changes unassociated with thrombi and emboli in the brains of man and experimental animals, such as the monkey, duck and chick, as shown in this paper, suggests that another mechanism may account for the pathogenesis of the hemorrhages present in the brain in cases of acute malarial infection.

The focal areas of necrosis observed in the brain of the child, monkey, duck and chick were similar to the lesions described by Dürck [6] and Margulis.[5] In the lesions described by Dürck, and now known as "Dürck granulomas" a large number of glia cells accompany the necrosis. It is suggested that a period must elapse to permit this glial reaction to occur.

The pathologic lesions in the brain of both man and the experimental animals infected with malaria are identical with changes in a series of animals which Hartman [18b] concluded to be the result of anoxia. It has been suggested by one of us (R. H. R.) that the pathologic lesions in the viscera of man, monkey and duck may be influenced in their development by anoxia.[20]

The patient whose brain was used for this study had only approximately 1,500,000 red blood cells at the time of death. In monkeys, likewise, rapid anemia developed. The red blood cells in the ducks frequently decreased within forty-eight hours from 2,200,000 to 600,000. This rapidly progressing anemia apparently was responsible for the anoxia. It is only reasonable to believe that because the malarial parasites utilize hemoglobin, parasitized red blood cells do not carry the same quantity of oxygen as nonparasitized cells. The myocardium may become anoxic and the circulation slowed, thus producing a stagnant type of anoxia. Anoxia therefore appears to be the basis for the development of the cerebral lesions in malaria.

19. Schüffner, W. A. P., and Esseveld, H.: Causes of Malignancy of Tropical Malaria, Geneesk. tijdschr. v. Nederl.-Indië **76**:3038-3045, 1936; abstracted, Trop. Dis. Bull. **34**:383, 1937. Cropper, J.: Phenomenal Abundance of Parasites in a Fatal Case of Pernicious Malaria, Lancet **2**:16-17, 1908.

20. Rigdon, R. H., and Stratman-Thomas, W. K.: A Study of the Pathological Lesions in P. Knowlesi Infection in M. Rhesus Monkeys, Am. J. Trop. Med. **22**:329-339, 1942. Rigdon, R. H.: A Pathological Study of the Acute Lesions Produced by P. Lophurae in Young White Pekin Ducks, ibid. **24**:371-377, 1944; footnote 14.

PATHOGENESIS OF LESIONS IN THE BRAIN ACCOMPANYING MALARIA

Our pathologic studies suggest that an increased permeability occurs in the capillaries of the brain in cases of severe malaria, as indicated by the enlargement of the perivascular and pericellular spaces (fig. 2*A*). This increase in permeability is the result of anoxia. Accompanying this increased permeability of the capillaries is anoxia of the adjacent parenchymatous tissue, as indicated by the focal changes in the myelin. Such foci are apparent from the variation in staining (fig. 3). As the process of anoxia continues the myelin in these focal areas degenerates. The permeability of the capillary walls may be sufficiently impaired to permit the escape of parasitized and nonparasitized red blood cells. Such cells may partially or completely fill the foci of myelin degeneration and may extend into the surrounding tissue, producing the classic petechiae, as observed with the severe types of malaria. With the lapse of time glial and mononuclear cells may proliferate in these areas of necrosis.

The cytologic changes as observed in the nerve cells of the cerebral cortex and the Purkinje cells of the cerebellum in this study are, in our opinion, also the result of anoxia.

Accompanying the development of the neurologic lesions are severe pathologic changes in the other viscera of the body. The myocardium and the peripheral circulation are severely affected, and the rate of circulation decreases throughout the brain. This slowing of the circulation increases the cerebral anoxia. The parasitized red cells apparently tend to localize along the wall of the capillaries and may interfere with the function of the endothelial cells. All the metabolic processes within the brain, therefore, may be progressively impaired until death results.

SUMMARY

The pathologic lesions occurring in the brain of a child who died in the acute stage of infection with P. falciparum and in brains of the monkey, duck and chick infected with malaria were similar. The gray and the white matter of the entire brain and spinal cord were sometimes involved; however, the cerebral hemispheres and the cerebellum showed the most extensive injury. These neurologic lesions may result from anoxia.

University of Arkansas School of Medicine.

CHARACTERISTIC ROENTGENOGRAPHIC CHANGES ASSOCIATED WITH TUBEROUS SCLEROSIS

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Knowledge of the presence of characteristic roentgenographic changes in the skull of patients with tuberous sclerosis has been a fairly recent addition to the diagnostic criteria of this disease entity. In 1924 Marcus[1] described the roentgenogram in a case of tuberous sclerosis, as follows:

> In several places within the cranium were calcified areas the size of a bean or pea, with layers of "chalk shale." Most such areas were located in the middle fossa on the left side, but several were visible in the parietal regions.

Dalsgaard-Nielsen stated that Marcus' case is the first published instance of tuberous sclerosis with roentgenographically discovered calcification in the cerebrum. In 1935 Dalsgaard-Nielsen[2] published the following description of the calcifications noted in roentgenograms of the skull of a 14 year old boy with convulsive seizures and adenoma sebaceum.

> The shape of the cranium is normal. The sella turcica is small but otherwise normal. Scattered throughout the roentgenogram of the skull are numerous osseous shadows. They are irregular in form and size and in great part slightly "watery," but their density is variable. No destruction of bone is seen. Many of these shadows are situated in the calvaria and may be assumed to be hyperostotic changes. Not a few are doubtless located in the cerebrum itself and appear there as spreading, small and irregular calcifications in the left hemisphere. One calcification lying at about the middle of the left frontal lobe is the size of an orange. The rest of the skeletal system shows no roentgenographic changes.

Later, Gottlieb and Lavine[3] described analogous roentgenographic changes in another case of tuberous sclerosis. Yakovlev and Corwin[4] reported the roentgenographic demonstration of multiple discrete areas of calcification throughout the brain. Heublein, Pendergrass and Widman[5] described the calcifications seen in their cases as being within the brain substance, and in 1 instance possibly within the calvaria. Pancoast, Pendergrass and Schaeffer[6] stated:

> . . . not infrequently the bones of the extremities and occasionally of the calvaria show changes which include periosteal deposits and cystic or "punched out" areas in the spongiosa.

In a recent publication, Ross and I[7] stated that the chief roentgenographic finding in tuberous sclerosis, that of patchy zones of increased density in the skull, is located in the calvaria. These zones occurred in half our cases. We have been unable to find any description of the structural changes which occasion this appearance.

One of the patients in our previous study known to be hemophilic, presented the characteristic roentgenographic features of tuberous sclerosis. Most of the diagnostic studies performed on the other patients in that series were omitted with this patient because of the difficulty in control of bleeding following such simple procedures as venipuncture and the withdrawal of blood from the finger tip for routine studies of the blood. The patient has since died, and autopsy was performed. We believe that the following presentation is the first detailed description of the location and nature of the structural changes giving rise to the roentgenographic lesions which he presented.

REPORT OF CASES

CASE 1.—*History.*—L. B., a white boy, was admitted to the Caro (Mich.) State Hospital for Epileptics on July 25, 1942; at that time he was 10 years of age. Both the paternal and the maternal branch of the family showed several neuropathic deviations. The mother had

From the Caro State Hospital for Epileptics; R. L. Dixon, Medical Superintendent.

1. Marcus, H., cited by Dalsgaard-Nielsen.[2]

2. Dalsgaard-Nielsen, T.: Tuberøs sclerose med sjaeldent røntgenfund, Nord med. tidskr. **10**:1541 (Sept. 28) 1935.

3. Gottlieb, A. S., and Lavine, G. R.: Tuberous Sclerosis with Unusual Lesions of the Bones, Arch. Neurol. & Psychiat. **33**:379 (Feb.) 1935.

4. Yakovlev, P. I., and Corwin, W.: A Roentgenographic Sign in Cases of Tuberous Sclerosis of Brain (Multiple "Brain Stones"), Arch. Neurol. & Psychiat. **42**:1030 (Dec.) 1939.

5. Heublein, G. W.; Pendergrass, E. P., and Widman, B. P.: Roentgenographic Findings in the Neurocutaneous Syndromes, Radiology **35**:701 (Dec.) 1940.

6. Pancoast, H. K.; Pendergrass, E. P., and Schaeffer, J. P.: The Head and Neck in Roentgen Diagnosis, Springfield, Ill., Charles C Thomas, Publisher, 1940, p. 663.

7. Ross, A. T., and Dickerson, W. W.: Tuberous Sclerosis, Arch. Neurol. & Psychiat. **50**:233 (Sept.) 1943.

fainting spells and was considered a religious fanatic. The father was described as mentally deficient. Our patient was the oldest of 5 children, the others apparently being normal. The birth and developmental histories were not unusual. At the age of 6 months he cut his mouth and bled for two weeks. He began to have convulsions a month later, and the attacks continued until his death. He was greatly retarded in walking and never learned to talk.

He was admitted to the University Hospital, Ann Arbor, Mich., when 3 years of age because of convulsions. There he was resistive to every examination. The general physical examination revealed nothing significant except for a scattered papular eruption over the body. The neurologic examination was unsatisfactory, and the reflexes were normal as far as could be determined. Ophthalmologic examination revealed nothing abnormal. All laboratory examinations, including studies of the spinal fluid, yielded normal results. Roentgenograms of the skull were considered to be within normal limits. A pneumoencephalogram showed moderate dilatation of the ventricles, slightly greater on the left side. The subarachnoid channels over the right cortex were incompletely drained. There was no gross displacement of the ventricular system. During his stay in the hospital he was given three small transfusions of blood because of long-continued hemorrhage from a laceration of the tongue which he received during a seizure. He was discharged without medication; the final diagnosis was grand mal epilepsy.

When 10 years of age he was admitted to a nursing home with second and third degree burns, which he had received in a seizure. They covered approximately one third of the body. In addition to his untidiness and restiveness, many hemorrhages from the granulating surfaces of the wounds added to the difficulties of his care. Four months later he was transferred to the Caro State Hospital.

Examination.—The patient was pale and underdeveloped, obviously at the idiot level of intelligence. He made no attempts to speak and drooled continually. There were many incompletely healed burns over the lower extremities and a slight contracture of the right knee. He was able to walk. Sebaceous adenomas were present in typical butterfly distribution over the nose, cheeks and nasolabial folds. There were three café au lait spots on the face: (1) one measuring 5 by 1.5 cm., extending from the brow to the hair line on the right side of the forehead; (2) one, measuring 1 by 0.75 cm., situated immediately above the right angle of the mouth, and (3) a similar spot on the left cheek, at the midpoint of the horizontal ramus of the mandible. The rest of the general physical examination revealed nothing significant. The neurologic examination showed only a Babinski sign on the left side. The ocular fundi could not be visualized. The kidneys were not palpable.

Routine laboratory examinations revealed only moderate secondary anemia. The Kahn reaction of the blood serum was negative. No other laboratory examination was attempted. Roentgenograms of the skull (fig. 1 *A*) demonstrated many islands of increased density throughout the cranium. In stereoscopic views these appeared to be within the calvaria. There was also a small area of increased density, of irregular outline, in the posterior fossa. Roentgenograms of the chest showed nothing abnormal.

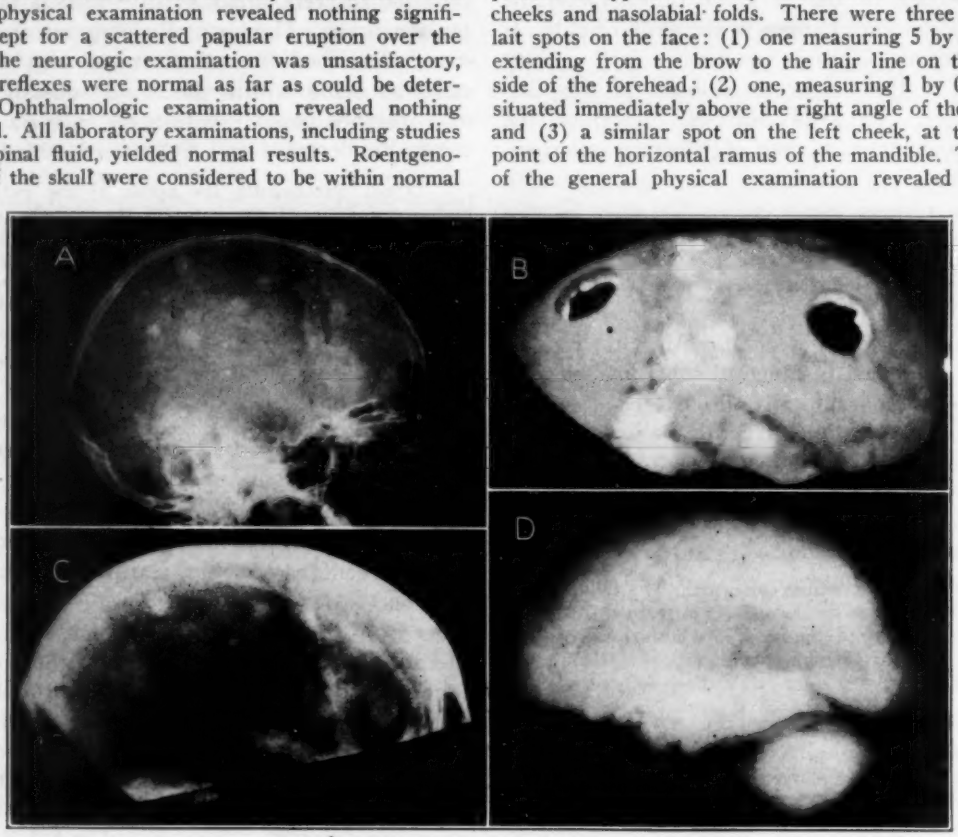

Fig. 1 (case 1).—*A*, roentgenogram of the skull in the lateral projection, demonstrating the islands of increased density which are the chief roentgenographic sign in cases of tuberous sclerosis. An indistinct area of increased density is also seen in the posterior fossa. *B*, photograph of the calvaria obtained by transillumination, demonstrating the increased translucency of the involved areas. The sites of removal of the buttons of bone for histologic examination were sealed with black photographic paper. *C*, roentgenogram of the calvaria, demonstrating that the islands of increased density are situated in the calvaria. *D*, roentgenogram of the brain. The islands of increased density seen in roentgenograms of the skull are not visible. The area of calcification seen in the posterior fossa in *A* appears here in the cerebellum. If the dense areas of the roentgenograms of the skull were due to calcification in or around the cortical nodules, they should also be visible here.

Course in the Hospital.—The patient continued to experience many convulsive attacks. He received several injuries during seizures; the slightest break in the skin or mucous membranes was always the site of a brisk hemorrhage. Injections of a solution of brain extract and a preparation of vitamin K were seldom successful in controlling the bleeding; he received three transfusions. He died suddenly, apparently in a seizure.

Autopsy.—General Observations: The skin and subcutaneous tissues of the face, neck, trunk and extremities showed pitting edema. Pigmented areas and sebaceous adenomas occurred on the face, as well as many healed scars on both lower extremities. The usual incision in the scalp bisected a plaque measuring 4 cm. in diameter and 0.5 cm. in thickness, of orange color and granular appearance, situated immediately to the right of the midline. Here and there in the calvaria could be seen areas, roughly circular in outline and varying from 0.3 to 1.5 cm. in diameter, of a deeper yellow than the surrounding bone; however, there was no change in the consistency of the bone. When the calvaria was removed, these areas were more translucent to light than the surrounding bone (fig. 1 *B*). On the inner surface, each of these areas was more grayish and was slightly indented below the level of the surrounding bone. The dura was approximately twice the normal thickness.

The abdominal cavity and the pericardial sac contained increased amounts of clear, straw-colored fluid. The spleen was large and boggy, weighing 260 Gm. The surfaces of both kidneys were studded with many small yellow tumors, varying from 0.3 to 1.5 cm. in diameter. At the upper pole of the right kidney there was a larger tumor mass, approximately the size of a silver dollar and 1 cm. in thickness. Two small subcapsular cysts were seen in the left kidney; within the substance of the left kidney was a tumor nodule, about 1 cm. in diameter.

Histologic Study (Dr. H. E. Cope, Michigan Department of Health): The lesion of the scalp was an old degenerating hematoma. A pigmented area from the right cheek contained numerous sebaceous glands, about which there was an inflammatory reaction of moderate intensity. The lungs exhibited moderate edema. Some sections of the liver contained many focal areas of infiltration with round cells and a moderate number of polymorphonuclear cells. This focal reaction was not periductal. The appearance of the spleen was not unusual. The renal tumors were made up of cells of varying size and shape, some of which resembled striated muscle. Other cells were not differentiated, and a few large multinucleated cells were seen. In the main, the tumors were fairly well differentiated and well encapsulated; they contained many thick-walled blood vessels.

The pathoanatomic diagnosis was rhabdomyomas of the kidneys, adenoma sebaceum, degenerating hematoma of the scalp, focal subacute hepatitis and pulmonary edema.

A roentgenogram of the calvarium (fig. 1 *C*) showed that the large areas of increased density seen in the roentgenograms of the skull were located within the calvaria. A roentgenogram of the brain after fixation (fig. 1 *D*) demonstrated that the islands of increased density which had been seen in roentgenograms taken during life and in roentgenograms of the calvaria were not visible. The calcified area seen in the posterior fossa in the roentgenograms of the skull was in the cerebellum.

Two buttons of bone were removed, each 2.5 cm. in diameter and each containing one of the areas in question, as confirmed by subsequent roentgenograms. These were examined by Dr. Carl V. Weller, of the department of pathology, University Hospital, Ann Arbor, Mich. His report follows.

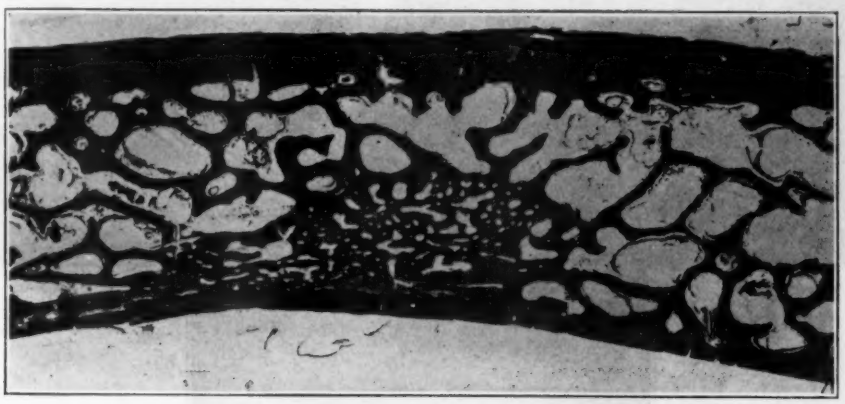

Fig. 2 (case 1).—Low power photomicrograph of a section from one of the islands of bone removed from the calvaria. Hyperostosis of the inner table and of the trabeculae of the diploic spaces is demonstrated. The normal bone marrow has been replaced by fat.

"The dense patches in this bone were areas of osteosclerosis, in which the marrow spaces of the cancellous bone of the diploic area had largely disappeared, owing to a concentric development of bone on the previous trabeculae (fig. 2). There was no evidence of neoplasm. It was evident that in the region of osteosclerosis the marrow was fatty instead of cellular. I am not prepared to make any suggestion as to why one region, rather than another, was selected for this change."

Brain: The brain was examined by Dr. Nathan Malamud, of the laboratory of neuropathology at the Neuropsychiatric Institute, Ann Arbor, Mich. His report follows.

"Gross examination: The brain was rather small. The leptomeninges were delicate, and on their removal the convolutional pattern of the brain was observed to be interrupted by pearly white, slightly raised, nodular patches of varying size, which were cartilaginous and hard, with roughened surface and occasionally umbilicated centers. These patches were scattered indiscriminately over the entire cerebrum but were most numerous in the frontal lobes. On the right side, five nodules were noted in the superior frontal gyrus; one each in the orbital, middle and inferior frontal gyri;

one in the postcentral gyrus parasagittally, and two in the angular and the lateral occipital gyrus respectively. On the left side, there were five nodules in the superior frontal gyrus, two in the middle frontal gyrus, one in the precentral gyrus, one in the superior parietal gyrus, one in the supramarginal gyrus, two large nodules in the middle temporal gyrus and one in the inferior temporal gyrus. No definite nodules could be made out on the inferior and median surfaces of the hemispheres. On section, the nodules were distinguished by their white surface and grayish centers, with poor demarcation between the cortex and the white matter. There was moderate hydrocephalus, and the ventricles were studded along their surfaces with numerous tumor nodules, resembling candle gutterings. The brain stem and the cerebellum were not grossly altered.

"Histologic examination: Tuberous nodules in the cortex showed characteristic delamination, decrease in the number of neurons, extensive gliosis and monster nerve and glial elements spreading into the white matter. Examination of the subependymal tumors showed extremely fibrous spongioblastomas, with considerable calcification. There were a few greatly calcified cerebellar nodules.

"The diagnosis was tuberous sclerosis."

An additional case (mentioned as case 2 in the previous paper[7]) likewise demonstrated that the areas of increased density in question are situated in the calvaria. A brief summary follows.

Case 2.—A woman aged 29, an Austrian Jew, had a feebleminded grandfather and two feebleminded sisters, neither of whom had convulsions or presented facial lesions. She had had a great number of grand and petit mal seizures since the age of 11 years. She had never talked, fed or dressed herself and was untidy. Her mental development was that of an idiot. She was physically underdeveloped and resistive; she usually sat cross-legged and made stereotyped rocking movements. Sebaceous adenomas were present over the face. She walked on everted feet. Both kidneys were palpable, the left seeming to be of normal size and the right slightly enlarged. The external rectus muscles were weak. Far out on the temporal portion of each ocular fundus were deposits of pigment, suggesting old chorioretinitis. On the medial margin of the patch in the right eye was a small, round, yellowish lesion with a nodular appearance. Neurologic examination revealed nothing abnormal.

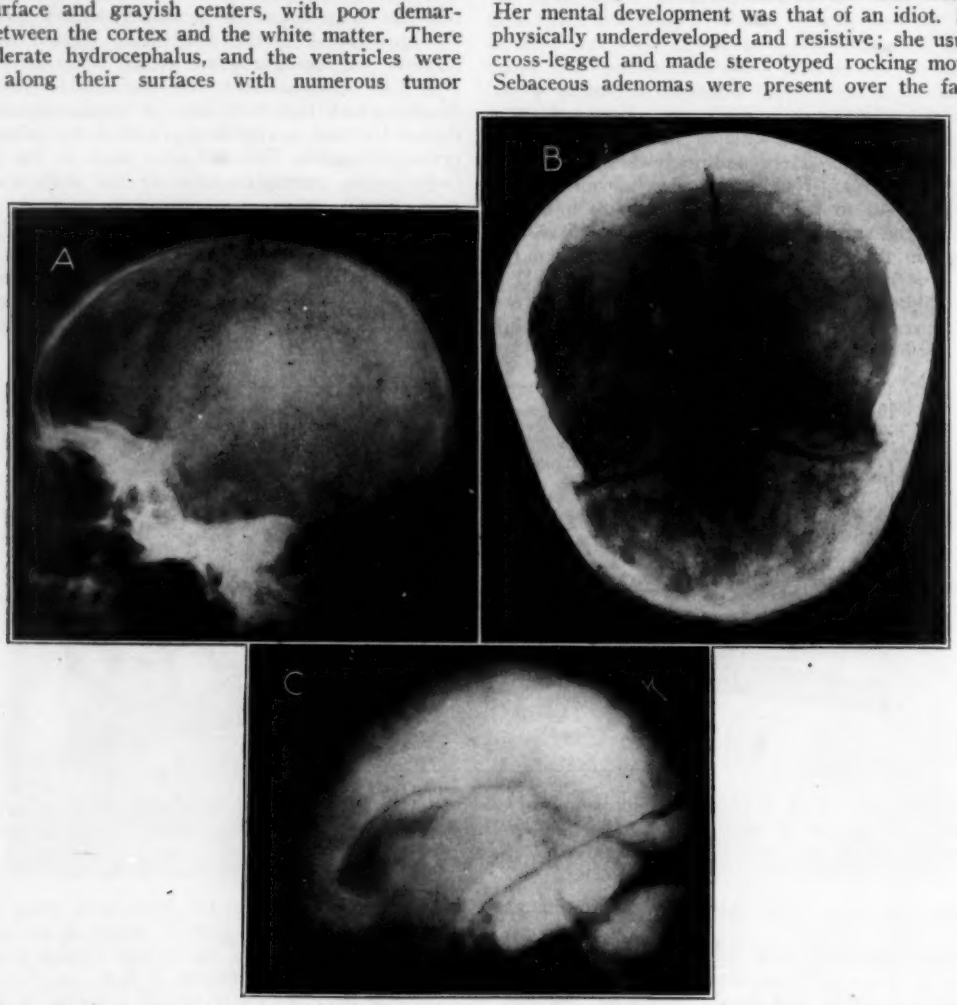

Fig. 3 (case 2).—*A*, roentgenogram of the skull in lateral projection, demonstrating the characteristic islands of increased density. *B*, roentgenogram of the calvaria (vertical projection). The islands of increased density seen in *A* are here present. *C*, roentgenogram of the brain after fixation. The islands of increased density are not visible.

Laboratory Data.—A complete blood count, a Kahn test of the blood and examination of the spinal fluid gave normal results. The urine contained a trace of albumin and a few granular casts. A biopsy specimen

taken from one of the facial lesions was diagnosed as "adenoma sebaceum."

Roentgenographic Findings.—Roentgenograms of the skull (fig. 3 *A*) showed patchy zones of increased density in the cranial vault, but there was no evidence of intracranial calcification. The flat bones of the skull were relatively thick. There appeared to be diminution in volume of the cranial cavity, similar to that seen in microcephaly. Pneumoencephalograms showed a generalized atrophy or hypoplasia of the brain.

Course in the Hospital.—Seizures recurred at irregular intervals. In the course of a year both kidneys, particularly the right, became considerably enlarged. The patient died of bronchopneumonia following a series of seizures.

Autopsy.—Examination of the brain post mortem confirmed the clinical diagnosis of tuberous sclerosis with subependymal tumors in the ventricles. Both kidneys were considerably enlarged; histologic examination gave a diagnosis of rhabdomyomas undergoing extensive fatty degeneration. A single roentgenogram of the calvaria taken in the vertical projection (fig. 3 *B*) confirmed the impression that there were patchy zones of increased density in the cranial vault. A single lateral roentgenogram (fig. 3 *C*) of the brain after fixation showed no demonstrable calcification.

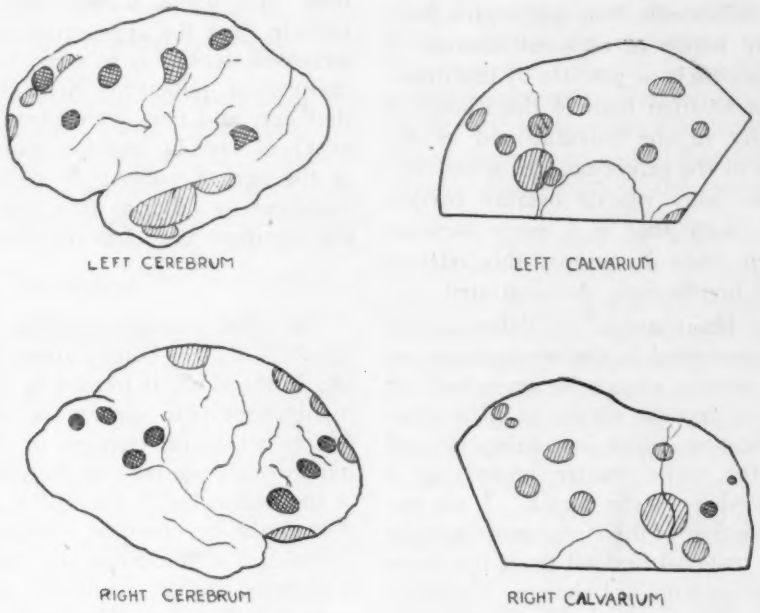

Fig. 4.—Line drawings showing the location of the cortical nodules in the cerebrum and of the involved areas in the calvaria. The cortical nodules indicated by cross hatching lay immediately beneath islands in the calvaria.

COMMENT

In previous publications, widely varying opinions have been expressed as to the nature and location of the characteristic calcifications seen in roentgenograms of the skulls of patients with tuberous sclerosis. Dalsgaard-Nielsen stated that some of them were purely hyperostotic formations of the internal lamina; he expressed the belief that others were apparently located within the brain itself. Gottlieb and Lavine reported thickening of the tables of the skull and a peculiar mottling, with indistinct islands of increased density alternating with areas of rarefaction. Yakovlev and Corwin attributed these areas of increased calcification to degenerative changes at the periphery of the tuberous nodules in the cerebral cortex.

My present study demonstrates that Dalsgaard-Nielsen's first statement was essentially correct. Figure 2 shows that the increased radiopacity was due chiefly to hyperostosis of the inner table of the calvaria, although the hyperostosis was not limited to that structure alone. The material obtained at autopsy in all 3 cases reported in the previous paper, as well as in the present case, showed small calcareous deposits throughout the subependymal nodules and basal ganglia; they were present in 80 per cent of the roentgenograms in the entire series of cases. Other investigators, as well as my colleagues and I, have mentioned that these deposits might be confused with other calcifications in the glomus of the choroid plexuses, basal ganglia and pineal body. They were not seen in the present case, either in roentgenograms obtained during life or in the roentgenograms of the brain after fixation. However, these deposits, when visible in roentgenograms, in no way resemble the larger areas in question and are not apt to be confused with them.

I am unable to demonstrate any rarefaction of the bone surrounding the islands of increased density, as suggested by Gottlieb and Lavine. If such areas were present, one would expect them to be less translucent to light than the surrounding bone; figure 1 *B* shows the reverse to be true. It appears that the increased translucency is due to two factors: (1) a diminution in the thickness of the bone in these areas and (2) replacement of normal bone marrow by fat in the involved areas. The latter also accounts for their gross appearance of being slightly more yellow than the surrounding bone.

Dalsgaard-Nielsen stated his belief that most areas of calcification were present within the neoformations of the cortex but that the hyperostoses in the internal lamina were independent processes; admittedly, they might arise from the local irritant action of adjacent tumors. I have recorded as closely as possible by line drawing (fig. 4) the location both of the islands of increased density in the calvaria and of the cortical nodules in the cerebrum. In a majority of instances the bony islands overlay cortical tumors. It is likely that if a more accurate record had been made at autopsy this relation would be more impressively demonstrated.

The "multiple brain stones" of Yakovlev and Corwin, as demonstrated in the roentgenograms shown in their article, cannot be accounted for by the calcareous deposits shown in their illustration of calcification, either in a subependymal nodule or in the white matter underlying a tuberosclerotic nodule in the cortex. I am unable to find that either of their photomicrographs was of autopsy material derived from the cases in which roentgenograms are shown. Calcification, to produce the typical roentgenographic appearance, would have to occur on the surface of the cortical nodules. My colleagues and I have not seen calcification within the "potato patches" or adjacent white matter in any of our 5 cases of tuberous sclerosis in which autopsy has been performed although 2 patients were well past the age of puberty; characteristic roentgenographic changes were present in 3 cases.

In our previous paper, Ross and I reviewed the cases of 12 patients from the Caro State Hospital, together with that of a new patient since admitted, whose roentgenograms of the skull showed the typical islands of increased bone density. No means were available by which the age at which the islands became visible in roentgenograms could be determined. However, the patients at the time the islands were discovered were all beyond the age of 10 years, the patient in the present case being the youngest. Of the 10 patients from the Caro State Hospital, together with 1 patient since admitted, in whose roentgenograms of the skull the islands were not seen, 7 were below the age of 8 years; the remaining 4 patients were 12, 17, 18 and 36 years of age respectively at the time of examination. It is likely, as suggested by Yakovlev and Corwin, that the appearance of these islands of increased density is in some way related to the changes of puberty. None were seen before that age, and they were present in 13 (76 per cent) of the 17 patients examined who were at the age of puberty or older. We have no comment to offer at this time with regard to the significance of this observation.

SUMMARY

The chief roentgenographic sign of tuberous sclerosis, that of patchy zones of increased density in the skull, is located in the calvaria. The roentgenographic appearance of these islands is due to structural changes in the bone, namely, hyperostosis not only of the inner table but also of the trabeculae of the diploic spaces. In addition to the hyperostotic changes, the calvaria is diminished in thickness, and the normal marrow is replaced by fat, rendering the involved areas more translucent to light and visible to the eye. There is no rarefaction of the surrounding bone. Many, if not all, of these islands overlie tuberous nodules in the cerebral cortex. The appearance of the islands of increased density seems to be in some way related to the changes of puberty; the reason for their appearance at this time remains unknown.

Caro State Hospital for Epileptics.

HEMIFACIAL SPASM

REVIEW OF ONE HUNDRED AND SIX CASES

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Hemifacial spasm is a minor, but distressing, neurologic disease. The records of 663 patients seen at the Mayo Clinic for various unwonted movements of the face have been reviewed; of these, 106 had cryptogenic hemifacial spasm. While we have been primarily interested in clarifying the prognosis, many other aspects of the disease are not generally recognized and will be dealt with.

Our reason for choosing the term hemifacial spasm from the many terms [1] available to describe this condition is simple. The disorder is a spasm that characteristically affects half the face. The alternate term facial hemispasm is incorrect because it is half the face which is affected by spasm, rather than half a spasm of the face.

Before the eighteenth century the term tic was applied to all abnormal movements of the face. André [2] first used the term tic douloureux for grimacing disorders of the face that were accompanied by pain, and the tics came to be separated into those which were painful and those which were not. Trousseau [3] separated from the larger body of painless movements those of a compulsive sort, and Charcot [2] demonstrated the significance of the psychic factor in this type.

Gowers [4] gave a description of facial spasm which leaves no doubt in the mind of the reader concerning his separation of tic from spasm and his segregation of hemifacial spasm from other spasms and convulsions. He stated that the spasm was usually clonic, that the orbicularis oculi was the muscle most often affected, that the frontalis muscle was rarely involved, that spasm of the stapedius muscle may be noted, that the spasm is met with only in adults, that in most of the cases the patients are women, that the spasm bears no relation to hysteria and that emotion and voluntary facial movements increase the spasm. Gowers did not ascribe much importance to reflex causes, as did Romberg,[5] and he discounted the importance of uterine disturbances and of von Graefe's [6] tender points in the distribution of the trigeminal nerve.

CAUSE OF THE SPASM

There has been much speculation on the probable site of the lesion responsible for hemifacial spasm. Previous to the turn of the century, a number of communications reported the occurrence of tumors and inflammations [7] in cases in which facial twitchings occurred, but such a causative agent is not common.

Of interest is the report of Gilbert, Cadiot and Roger [2] describing a dog that had spasmodic twitches of one ear considered to be similar to facial twitches in man. Successive removals of cortex, corpus striatum and cerebellum failed to affect the twitches, but destruction of the homolateral facial nucleus abolished them. Eight years later Habel [8] recorded the case of a woman who did not experience any change in a hemifacial spasm after the development of homolateral hemi-

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1. *Tic convulsif;* reflex facial spasm; hemispasm; the seventh disease; chronic faciospasm; nictitating spasm.

2. Cited by Meige, H., and Feindel, E. C. L.: Tics, and Their Treatment, translated and edited by S. A. K. Wilson, London, S. Appleton, 1907.

3. Trousseau, A.: Lectures on Clinical Medicine, translated and edited with notes and appendixes by P. V. Bazire, London, The New Sydenham Society, 1867, vol. 1, p. 428.

4. Gowers, W. R.: A Manual of Diseases of the Nervous System, Philadelphia, P. Blakiston's Son & Co., 1888.

5. Romberg, M. H.: A Manual of Nervous Diseases of Man, translated and edited by E. H. Sieveking, London, The Sydenham Society, 1853, vol. 1, pp. 290-298.

6. Cited by Russell.[7a]

7. (*a*) Russell, J. S. R.: Facial Spasm, in Allbutt, C., and Rolleston, H. D.: A System of Medicine, ed. 2, London, Macmillan and Company, Ltd., 1910, vol. 8, pp. 638-649. (*b*) Schultze, F.: Linksseitiger Facialiskrampf in Folge eines Aneurysma der Arteria vertebralis sinistra, Virchows Arch. f. path. Anat. **65**:385-391, 1875. (*c*) André-Thomas, cited by Gordon.[10b]

8. Habel, A.: Ueber Fortbestehen von Tic convulsif bei gleichseitiger Hemiplegie, Deutsche med. Wchnschr. **24**:189 (March 24) 1898.

plegia from cerebral vascular disease. The inference to be drawn was that the lesion lay in the nucleus of the facial nerve or distal to it. Babinski [9] expressed the opinion that the lesion is an irritative one in the peripheral course of the seventh nerve.

Some authors [7a] have claimed that the lesion was in the facial representation of the cortex; but, as Russell [7a] said, that hemifacial spasm should be "repeated time after time and year after year, and be confined to the anatomical distribution of a single nerve without further spread, and without causing even temporary paresis following the spasms, is contrary to the best established doctrines of discharging lesions of the cortex. . . . the most probable view is . . . that the facial nucleus in the pons is the starting point of the discharges which result in the spasms."

A historically important view [10] is one ascribing the abnormal movements to "reflex irritation." Brissaud [2] proposed that the term "spasm" be limited to "the result of sudden transitory irritation of any point of a reflex arc." He expressed the opinion that "reflex irritation" (in the distribution of the trigeminal nerve) explains a large body of facial spasms. Hunt [11] sponsored the view that the twitching was due to irritation of the afferent system of the facial nerve. Wilson [12] pointed out that afferent stimulation seldom produces the continuous spasms observed clinically but that it is possible that irritation of the facial nerve itself might result in antidromic conduction to the nucleus with the production of some abnormal condition there, which might then produce the spasms. However, he favored the view that direct irritation of the nerve or of its nucleus lay behind the spasm. The tendency for the development of contracture and weakness in the affected side of the face in cases of a long-standing condition led Harris and Wright [13] to the conclusion that the essential lesion is in the lower facial neuron.

9. Babinski, cited by Gordon, A.: Convulsive Movements of the Face: Their Differential Diagnosis; Effect of Alcoholic Injections, J. A. M. A. **58**:97-102 (Jan. 13) 1912.

10. (*a*) Dorrance, G. M.: New Method of Injecting Facial Nerve for Relief of Facial Spasm, J. A. M. A. **67**:1587-1589 (Nov. 25) 1916. (*b*) Gordon, A.: Tic and Spasm of the Face: Differential Diagnosis; Effect of Alcoholic Injections, Tr. Coll. Physicians Philadelphia **34**:313-321, 1912. (*c*) Ross, J.: A Treatise on the Diseases of the Nervous System, New York, William Wood & Co., 1881, vol. 1. Romberg.[5]

11. Hunt, J. R.: The Sensory System of the Facial Nerve and Its Symptomatology, J. Nerv. & Ment. Dis. **36**:321-350 (June) 1909.

12. Wilson, S. A. K.: Neurology, Baltimore, Williams & Wilkins Company, 1940, vol. 1.

13. Harris, W., and Wright, A. D.: Treatment of Clonic Facial Spasm: (*a*) By Alcohol Injection; (*b*) By Nerve Anastomosis, Lancet **1**:657-662 (March 26) 1932.

OBSERVATIONS

No case was accepted for this study in which there was evidence of a gross pathologic lesion in the posterior fossa or the peripheral course of the facial nerve. We are impressed with the ease with which hemifacial spasm may be differentiated from other twitching disturbances of the face.

Age.—The ages of onset ranged from 17 to 70 years, with a mean age of 45 years and a standard deviation of 12 years. There was no difference in the ages of onset in the two sexes. No report with which we are familiar records a case in which the age of the patient was less than 20 years. One of our patients began to experience the spasms at the age of 17; another, at 19, and a third, shortly after her twentieth birthday.

Sex.—Sixty-four of our patients were women, and 42 were men, thus confirming the observations of other authors [14] regarding the sex distribution.

Side of Face Affected.—In neither sex was one side of the face affected more often than the other.

Location at Onset.—For 7 patients we have no definite information as to the exact location of onset of the twitching. In all but 9 of the remaining 99 patients the muscles of the eyelids were involved early. Sixty-nine patients described their spasm as beginning in the eyelids; 7 patients, in the upper lid, and 18 patients, in the lower lid alone, while in 21 patients the involvement ranged from the eyelids and "quivering in the ear drum" to twitching of the whole side of the face. The reason for the high incidence of early involvement of the lids is not known. Gowers [4] explained the proneness to spasm in the orbicularis oculi muscle by saying that the "motor mechanism of this muscle is more sensitive, in consequence of its energetic reflex action." Oppenheim [15] and other authors [16]

14. Remak, E.: Localized Spasm, in Church, A.: Diseases of the Nervous System, New York, D. Appleton and Company, 1910, pp. 933-959. Gowers.[4] Russell.[7a]

15. Oppenheim, H.: Textbook of Nervous Diseases for Physicians and Students, ed. 5, translated by A. Bruce, New York, G. E. Stechert & Company, 1911, vol. 2, p. 1237.

16. Adson, A. W.: Neurosurgical Treatment of Muscular Spasms and Spastic Painful and Trophic Lesions of the Extremities, S. Clin. North America **13**: 895-904 (Aug.) 1933.

accepted this explanation without modification. In 9 of our patients the spasms did not start in the eyelids, and in 2 of these persons the lids never became involved.

Spread of Spasm.—The spasm usually spreads to adjacent muscles first, perhaps as a result of involvement of the corresponding and contiguously placed nerve cells in the nucleus of the nerve. Possible exceptions were the 9 patients who had only twitching of the orbicularis oculi muscle and drumming, popping or "motor boat" noise in the ears and the 21 patients who had only spasms of the platysma and orbicularis muscles. Thirteen patients eventually suffered from spasms of all the muscles of one side of the face, but, curiously, only 1 of these heard noises in the ear. Sixteen patients of the entire group did not note any spread of the spasm after the onset.

Bilateral Spasm.—Six patients, 5 of them women, had bilateral spasms. The time interval between onset on one side and onset on the other ranged from less than a year to fifteen years. In no patient were the spasms synchronous or symmetric, and in none did the severity or extent of the spasms on the side secondarily involved overtake those on the side primarily involved.

Type of Spasm.—The lay term "twitching" describes the movements rather well. They consist of an intermittent and wholly irregular series of single muscle twitches, coming in rapid sequence and involving but a fraction of the muscle fibers of any one muscle in any one twitch. Twenty-one patients suffered from both twitches and sustained spasm, and in most of the attacks the twitchings increased periodically in frequency and intensity until, at the climax, there was a sustained spasm, lasting from a few seconds to a minute. In 1 patient the onset was with sustained spasm, followed by twitching. Four patients had sustained spasms alone, and the duration of these spasms ranged from a few seconds to five minutes, the length of the spasm being fairly constant in each patient.

Persistence in Sleep.—Twelve patients reported that the twitching had been observed in sleep, and 5 of these patients complained that on occasion they had been awakened by the twitching. Thirty-nine patients had been observed in sleep and reported that spasms were then absent.

Remissions.—Nine patients experienced one or more periods of complete freedom from spasms, lasting from a few weeks to three years. One of these patients experienced a three year period of freedom following gastroenterostomy. Another patient had two years of freedom following refraction and use of glasses.

Provocative Circumstances. — Circumstances said by the patients to increase the severity of the spasms or to precipitate their appearance occurred with the following frequencies: nervous tensions of various sorts, 54 patients; fatigue, 29 patients; voluntary movement of the face, 23 patients; "excessive" use of the eyes, 11 patients; being under observation by others, 9 patients; being with other people, emotion, thinking and talking about the spasm, and menstruation, 4 patients each; concentration, 3 patients; quiet and cold, damp weather, 2 patients each; warm weather, shaving, trying to go to sleep, coitus, talking to "bothersome people," excessive smoking, constipation, loss of sleep and eating sweet and sour foods, 1 patient each. It is apparent that psychic factors have considerable influence on these spasms; yet the influence is of such a character, as will be pointed out later, that it does not cause confusion with the true tics.

Ameliorating Circumstances.—Only 21 patients had discovered circumstances which definitely benefited them. Among these circumstances were solitude, pressure below the lobe of the ear, massage, fatigue, work, relaxation, plenty of sleep, quiet, going away from home, physical activity, coitus, being outdoors and reading an interesting book. Three patients claimed to have some voluntary control of the spasms. The story was the same for all: An effort to relax the face resulted in momentary and slight diminution of spasm.

Neurologic Examination.—In 41 of our patients some abnormality was noted in addition to the spasms. Facial weakness and contracture were observed rather frequently. Weakness was noted in 16 patients, and only on the side of the spasm, except in 1 patient, who had had Bell's palsy of the opposite side several years previously. The importance of contracture has been mentioned in reports[17] dealing with the treatment of the spasm by interruption of the nerve, since the contracture prevents the palsy from being as disfiguring as it might otherwise be.

Partial deafness was another rather frequent finding. In 14 patients hearing was impaired on the side involved by spasm; in 3 patients there was deafness on the opposite side, and 1 patient was somewhat deaf in both ears, but more so on the side of the spasm than on the opposite side.

17. Coleman, C. C.: Surgical Treatment of Facial Spasm, Ann. Surg. **105**:647-657 (May) 1937.

Two patients complained of vertigo. One of these patients had had vertigo for a number of years before the onset of the spasm. Five years later the vertigo disappeared without treatment, but not so the spasm. The other patient had a single attack of vertigo two weeks after the onset of the spasm. Two patients had a homolateral increase of lacrimation.

Two patients had pupillary irregularity; 3, anisocoria; 1, faulty convergence; 2, tremors of the extremities, and 1, cogwheel rigidity of the contralateral arm. Two patients exhibited diminution of the homolateral corneal reflex without demonstrable weakness of the orbicularis muscle. Encountered in 1 patient each were occasional numbness of the homolateral side of the upper lip, mild numbness of the face associated with the more severe twitches, homolateral pathologic plantar reflexes, contralateral pathologic plantar reflexes, contralateral superior laryngeal paralysis, diminution of vibratory sensibility in the homolateral leg, diminution of taste on the homolateral side of the tongue, weakness of the homolateral side of the tongue and diminution of the ankle jerk and of vibratory sensibility in the contralateral leg.

One of our patients was hemiplegic and resembled the patient described by Habel.[8] She suffered from hypertension and began to have left hemifacial spasm at the age of 43 years. Five years later a stroke resulted in severe left hemiplegia, which included the face. The spasm was affected thereby little, or not at all, and when the patient was observed at the clinic a year later the hemiplegia and an unabated hemispasm of the face were still present.

Pathologic Study.—No patient died while under our observation, and therefore we have no necropsy observations to report. Wilson[12] was not aware of any instance in which the brain of a patient with this condition had been subjected to examination by modern pathologic technics. Either investigators in the past did not note anything to account for the spasms, or they encountered gross progressive lesions, such as tumors and aneurysms. Hemifacial spasm is a thing apart from symptomatic facial twitchings due to irritation by such lesions.

Associated Diseases.—It has been suggested[18] that hemifacial spasm is in some instances a manifestation of encephalitis. In 1910 Russell[7a] stated that the condition was rare before the age of 45 years. About half of our patients were less than this age. If encephalitis is a prominent cause, it would explain the high incidence of the condition among our patients in the younger age group, since the pandemic of encephalitis at the close of the war of 1914-1918 affected our group, but not Russell's. One might expect to find, also, a significant time relation in our cases with respect to the years of prevalent encephalitis. Forty of our 106 patients gave a history of having had influenza and the related illnesses in the period from 1919 to 1923. The percentage of patients giving a history of influenza was essentially the same for each half-decade of onset; and there was no peak at a certain interval after the pandemic, as would be expected if this factor were operative. Neither was the age of onset in the group giving a history of influenza different from that of the group as a whole. Only 1 patient gave a straightforward story of hemifacial spasm originating in an episode suggestive of encephalitic disorder.

Forty-one patients had anatomic evidence of arteriosclerosis. Thirty-seven of 92 patients whose eyegrounds were examined had evidence of arteriosclerosis there, but in 7 patients the changes were slight and were not associated with hypertension. Four patients had evidence of coronary or peripheral sclerosis. None of these patients was less than 35 years of age. Fortunately, for our purposes, a previous study[19] had been made of the blood pressures of nearly 1,000 patients who had registered consecutively at the clinic. The accompanying table compares

Percentage of Hypertension Among Patients with Hemifacial Spasm and Among Controls

	Number of Patients	Percentage Having Systolic Blood Pressure of: More Than 144 Mm. Hg	More Than 159 Mm. Hg
Controls less than 50 years of age	606	9.1	5.4
Patients less than 50 years of age having spasm	39	15.3	5.1
Controls more than 50 years of age	369	37.9	27.4
Patients more than 50 years of age having spasm	61	39.3	32.8

the data for the blood pressures of this random group and the pressures for patients who had hemifacial spasm. It is barely possible that hypertension is more common among patients with spasm who were less than 50 years of age than among other patients of the clinic of corresponding age (who probably have a higher incidence of hypertension than the population at large), but statistically the difference is not significant.

18. Gordon.[10b] Harris and Wright.[13]

19. Braasch, W. F.; Walters, W., and Hammer, H. J.: Hypertension and the Surgical Kidney, J. A. M. A. **115**:1837-1841 (Nov. 30) 1940.

Remak [14] associated migraine with hemifacial spasm in his account of the condition. Thirty of our patients had headaches of varying descriptions, and for 16 of these a diagnosis of migraine was made. The association remains obscure.

As a condition associated with hemifacial spasm some authors [20] have mentioned trigeminal neuralgia. Three patients in our series had hemifacial spasm associated with trigeminal neuralgia.

A woman, aged 70 when she came to the clinic, had begun to have trigeminal neuralgia of the right side of the face at the age of 55 years. Ten years later there developed rapid and intermittent twitches of the muscles of the right side of the face, which were more pronounced about the angle of the mouth and in the platysma muscle than elsewhere. Section of the posterior root of the affected trigeminal nerve gave complete relief of pain but only slight diminution of the severity of the spasm.

A man aged 21 had had trigeminal neuralgia of the right side of the face for fifteen months. Injection of alcohol into the fifth nerve gave complete relief for four years, when the pain returned in identical form. After about three months he noted slackening of the pain, though he was not undergoing any treatment, and as the pain disappeared there began an intermittent twitching of the right eyelid, which continued without modification for eighteen months.

A woman, aged 60 when she came to the clinic, first had noted twitching of the left eyelids at the age of 45. This continued without significant change for thirteen years, when there began typical neuralgic pains in the mandibular division of the left trigeminal nerve.

It will be noted that in each case the spasm was on the side of the face involved by the neuralgia, a curious association mentioned by Harris and Wright.[13] In the first case the neuralgia antedated the spasm by ten years; in the third case the spasm antedated the neuralgia by thirteen years. It is also of interest that in the first case, even though the pain was relieved, the spasm persisted. The slight improvement of the spasm may be accounted for by the disappearance of the pain and attendant worry, which, like any other discomfort or unnerving experience, may exaggerate an established spasm.

Injuries of the facial nerve of one sort or another have been said to be related etiologically to hemifacial spasm.[21] Movements resulting from faulty regeneration of a damaged facial nerve must be distinguished from hemifacial spasm. Our series included 3 patients whose spasm was preceded by facial paralysis. Two of these patients had the hemifacial spasm on the side that had been paralyzed, but there was nothing about either condition to suggest that the twitchings were of the associated movement type. In the third patient the spasm developed on the side opposite that previously paralyzed, and the faulty regeneration on the side that had been paralyzed verified the patient's story.

Six patients of the series were psychoneurotic. Five patients were rather definite in ascribing the onset of the twitching to psychic causes. These included a broken engagement, persecution as pro-German in 1917 and difficulties with husband and children.

Other diagnoses of associated diseases in the patients of this series were: obesity, 8 patients; infection of teeth, tonsils or prostate, 6 patients; cerebral arteriosclerosis, 4 patients; benign frontal hyperostosis, 3 patients; meningovascular syphilis, 2 patients; latent syphilis, 2 patients, and diabetes, 2 patients. One patient was found to have a concentration of calcium of 8.5 mg. per hundred cubic centimeters of serum but was not benefited by the elevation of the concentration to 12 mg.

DIAGNOSIS

Hemifacial spasm is a condition which, in the great majority of cases, may be diagnosed without difficulty provided the various simulating disorders are kept in mind. Of importance in clinical recognition are the following characteristics: 1. The spasms are of an intermittent twitching nature, such as might be encountered in intermittent faradization of the facial nerve. 2. The eyelids on the side are almost always involved. 3. The spasms are usually unilateral, and when they are bilateral they are not synchronous or equal in extent or severity. 4. The spasms may persist in sleep. 5. The patient does not feel any compulsion to make the movement. 6. The patient is unable to stop the movement by exercise of the will. 7. The patient cannot reproduce the movements voluntarily—especially is he unable to approach the speed with which the fine twitchings occur. 8. Psychic upsets of any sort, fatigue and voluntary movements of the face make the spasms worse. 9. Children do not have hemifacial spasm. 10. The spasms are limited to the muscles innervated by the facial nerve.

Symptomatic spasm due to gross disease in the posterior fossa or along the course of the seventh nerve is recognized by the presence of other signs, in addition to those associated with hemifacial spasm. True tic is distinguished by the involvement of muscles other than those receiving innervation from the seventh cranial nerve, by its frequent onset in childhood, by its variability, by the substitution of one tic for another, by the ease with which the spasm may be reproduced voluntarily, by the fundamental compulsion that the patient feels to make the movement, by the essentially purposive character of the act and by the ability of the victim to

20. Harris and Wright.[13] Oppenheim.[15]

21. Romberg.[5] Russell.[7a] Gordon.[10b] Harris and Wright.[13]

control the movement for a short period. The facial grimace of trigeminal neuralgia is present only with the pain. Facial paraspasm is symmetric, bilateral and predominantly tonic, often affecting the tongue and other bulbar muscles and often ceasing when the patient whistles, sings or chews some object, such as a toothpick.[22] Jacksonian epilepsy may show postconvulsive paresis and gross and clonic contractions, rather than rapid fine twitches and occasional spread of the convulsion. Faulty regeneration sequential to trauma of the facial nerve is recognized by the history of facial paralysis prior to the onset of the spasm and the simultaneous occurrence of slight twitches in some other part of the face associated with voluntary or emotional movements of another part.

TREATMENT

If one were to estimate the number of the various therapeutic procedures recommended at one time or another for hemifacial spasm, it is likely that the figure would compare not unfavorably with a similar total for any other disease of man or beast. Gowers'[4] list is representative. The variety of medicines tried with our series of patients is sufficient evidence that none was of outstanding benefit. One large group of patients received a mild sedative and was advised that more rest was in order. Another group received drugs of the belladonna series, and a few patients, ephedrine, sedatives and vaccines in addition. Other measures included reduction of weight and administration of benzedrine, iodides and diphenylhydantoin (dilantin) sodium.

Patients suffered enough from spasmodic disturbances of the face to undergo surgical operations even before the middle of the nineteenth century,[5] for Guerin and Moreau divided nerves of the face about 1780, while Dieffenbach[5] performed subcutaneous division of the muscle about the orbit, with good results, in a particularly stubborn case of hemifacial spasm in 1841. Nine of our patients underwent surgical procedures of one sort or another, 1 each having retrogasserian rhizotomy, thyroidectomy, injection of alcohol into the facial nerve and injection of procaine hydrochloride into the facial nerve. The procaine was injected preliminary to a proposed injection of alcohol, but the patient was so disturbed by the resulting palsy that nothing further was done. Two patients had diseased teeth and tonsils removed. Three patients were treated by anastomosis of the distal end of the facial nerve with the central end of the spinal accessory nerve.

Information is available for 73 patients on the results of treatment. Six patients died—stroke, cancer and coronary disease being the cause of death of the 3 patients for whom the cause is known. Thirty-nine patients stated that their spasms were unchanged or worse. Twenty-three patients reported moderate improvement; 2 of these are now dead. Only 8 patients were entirely relieved; 1 of these is now dead. Of the 8 patients who were relieved of spasm, 3 were treated by spinofacial anastomosis, with uniformly satisfactory results. Detailed consideration of the technic and of the results to be expected may be found in the communications of other investigators.[23] A variety of treatments were used for the other 5 patients who reported cures. One has been free of spasm for eight years after tonsillectomy and vaccine treatment. One patient experienced relief two months after leaving the clinic under a regimen including reduction of weight, a hot bath each night and administration of salicylates which had been ordered for an unrelated orthopedic condition. One patient reported that she had been free of spasm for three months after the use of thiamine and riboflavin, as ordered by her local physician. One patient had relief from 1933 until his death, in 1940, from injection of alcohol into the facial nerve. One patient's spasm stopped without any treatment. We are inclined to regard the outcome for 3 of these patients as uncertain, since a number of other patients experienced remarkable remissions only to have the spasms recur. It is apparent that little or nothing is to be expected from the use of drugs. Sedatives may modify the disturbance favorably to a slight degree.

Surgical treatment appears to offer the best prospects of obtaining relief and, after conservative measures have failed, should be offered to more patients than has been done. The patient may be told that an operation will relieve the spasm completely but at the cost of a variable period of complete paralysis followed by a longer period during which facial movements are associated with movements of the shoulder or tongue, depending on the operation chosen. If a large portion of the face is involved in the spasm, anastomosis is preferable to injection into the

22. Parker, H. L.: Bilateral Facial Spasm (Paraspasme Bilatéral of Sicard), Arch. Neurol. & Psychiat. **28**:1226-1227 (Nov.) 1932.

23. Gibson, A.: Facial Paralysis, Surg., Gynec. & Obst. **33**:472-489 (Nov.) 1921. Phillips, G.: The Treatment of Clonic Facial Spasm by Nerve Anastomosis, M. J. Australia **1**:624-626 (April 2) 1938. Gilbert, Cadiot and Rogers.[2] Adson.[16] Coleman.[17]

nerve or neurotomy, but the operation should be preceded by a trial of narcotization with procaine to be certain that the patient understands the implications of facial paralysis. Patients who have limited spasms, such as persistent twitching about the eye, are perhaps best managed by some sort of local denervation of the muscles affected, though we have not tried this.

COMMENT

Though abnormal movements of the face may be seen with a variety of lesions in the nervous system, it is altogether unlikely that hemifacial spasm may be caused by lesions in any supranuclear part of the pathway having to do with movements of the face. Our case in which hemiplegia, presumably due to capsular infarction, failed to affect the spasm and a similar case of Habel's constitute evidence that the lesion is not situated in the corticobulbar pathway. It is probable that there are other, uncharted, pathways from the higher centers to the facial nuclei, since certain patients with supranuclear lesions have paralysis of voluntary facial movement but not of emotional movement, and it may be possible that the spasmogenic lesion lies in these other pathways. However, a number of circumstances point rather definitely to the final common path to the facial muscles themselves as the site of the lesion. Perhaps the hardest circumstance to gainsay is the invariable confinement of the spasms to the muscles innervated by the facial nerve. The lesion in hemifacial spasm appears to be progressive, and it is difficult to understand why a lesion situated in the corticobulbar pathway would fail to implicate other muscles in at least a few cases. The frequent weakness and contracture of muscles supplied by the facial nerve speak strongly for disease of the lower motor neuron. Finally, there is the undeniable fact that gross lesions of the lower facial neuron can and do cause a twitching of the face very much like, if not actually indistinguishable from, the twitching of cryptogenic spasm and that the differentiation of symptomatic and cryptogenic spasm must be made on the basis of other evidence of disease of the posterior fossa or the peripheral nerve. The closest approach that can be made to the duplication of hemifacial spasm lies in irregular faradization of the facial nerve itself.

It can be stated with some assurance that the lesion does not lie distal to the exit of the nerve from the stylomastoid foramen, for section at this point and anastomosis with another cranial nerve result in reinnervation of the face with no recurrence of the twitching. Interruption of the facial nerve with subsequent regeneration of the fibers within the facial nerve itself almost always results in return of the spasm.

It appears, then, that the lesion is somewhere between the facial nucleus and the stylomastoid foramen. Thorough histologic examination of this segment of the facial pathway in a victim of hemifacial spasm may settle the question.

CONCLUSIONS

On the basis of the study of 106 patients with hemifacial spasm among 663 patients with pathologic movements of the face of all sorts, the following conclusions are drawn:

1. Women are more often afflicted than men, in the ratio of about 6 to 4.

2. Children do not have hemifacial spasm.

3. Encephalitic illnesses or arteriosclerosis, with or without hypertension, seldom bears a causal relation to hemifacial spasm.

4. The spasms usually begin in one orbicularis oculi muscle and slowly progress to adjacent muscles until, in certain cases, the entire facial musculature is involved.

5. Spontaneous remissions for periods up to three years have been noted.

6. The spasms in almost every case were aggravated by circumstances causing nervousness, fatigue or voluntary movements of the face.

7. No patient was able to stop the spasms by an exercise of the will.

8. Only 5 patients were seemingly cured without resort to surgical treatment, and 3 of these may well be in periods of remission.

9. Spinofacial anastomosis was performed on 3 patients, with satisfactory results in all.

10. There is evidence for the view that the lesion causing this condition is in the facial nucleus or the proximal portion of the facial nerve.

The Mayo Clinic.

METRAZOL AND ELECTRIC CONVULSIVE THERAPY OF THE AFFECTIVE PSYCHOSES

A CONTROLLED SERIES OF OBSERVATIONS COVERING A PERIOD OF FIVE YEARS

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The longer follow-up period and the larger number of patients warrant our present attempt to deal with some of the controversial aspects of convulsive shock therapy not adequately met by earlier studies.

MATERIAL AND PROCEDURE

The procedure is essentially similar to that employed in our first two studies.[1] A comparison is made of the results obtained with treated and with untreated patients with affective psychoses who were seen in private practice in the five years between July 1, 1938 and July 1, 1943. Of a total of 278 such patients, 81 were excluded because of incomplete or complicating data. Follow-up observations were conducted from December 1943 to March 1944, by means of telephone, letter or personal interview. The follow-up period ranged from six to sixty-nine months, with an average of forty months.

Of the 88 patients treated, the first 58 received metrazol and the other 30 were given electric shock therapy. The untreated, or control, group included 109 patients, of whom 43 refused convulsive therapy, 50 had symptoms which were too mild to warrant this treatment and 16 had physical disease which contraindicated use of the method. A comparison of the results for the treated and the untreated patients favors the controls with respect to spontaneity of remissions (table 1), mainly because of the mild character of the illness of many of the untreated patients. All of the treated patients, but only 30 per cent of the control patients, were hospitalized. All our patients, the treated and the untreated alike, were examined and observed over the same period by us.

RESULTS

Immediate and Follow-Up Results of Treatment.

TABLE 1.—*Comparison of Clinical Data for Patients Given Convulsive Therapy and for a Control Series*

	Number of Patients		Percentage of Patients	
	Treated	Untreated	Treated	Untreated
Sex				
Male	33	36	37	33
Female	55	73	63	67
Body build				
Pyknic	58	55	74	63
Asthenic	8	16	11	18
Athletic	12	8	15	9.5
Mixed	..	8	..	9.5
Diagnosis				
Involutional melancholia	22	16	25	14
Manic-depressive depression	51	84	58	77
Manic-depressive mania	15	9	17	9
Severity of illness				
Severe	20	16	23	14
Moderate	67	55	76	51
Mild	1	38	1	35
Previous attacks	49	62	55	57
Prepsychotic personality				
Extraverts	79	94	91	88
Introverts	8	13	9	12
Previous poor health	13	12	16	11
Associated physical disability	19	19	24	18
Positive family history	34	44	41	42
Precipitating episodes	35	41	41	37
Psychoneurotic reaction	18	27	23	24
Somatic delusions	14	7	16	7
Nihilistic delusions	6	5	7	5
Hallucinations	12	11	14	11
Paranoid trends	28	17	33	18
Feelings of depersonalization	8	7	10	7
Erotic reactions	9	3	11	3
Misidentification	7	..	8	..
Catatonic features	4	2	5	2
Destructiveness	9	1	11	1
Violence	5	2	6	2
Fear	39	18	46	17
Poverty of thought with monotonous speech	13	9	15	9
Suicidal tendency	34	35	40	32
Inaccessibility	15	10	18	10
Mutism	1	2	1	2
Lack of insight	46	33	51	30
		Treated		Untreated
Average age		42.5 yr.		43.8 yr.
Average duration of illness before examination		6.4 mo.		9.7 mo.
Average period of follow-up observation		40.0 mo.		39.0 mo.

1. The course of illness was shortened (table 2). This is apparent from the fact that

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1. Ziskind, E.; Somerfeld-Ziskind, E., and Ziskind, L.: Metrazol Therapy in the Affective Psychoses: Study of a Controlled Series of Cases, J. Nerv. & Ment. Dis. **95**:460 (April) 1942; Convulsive Therapy (Metrazol) in the Affective Psychoses: A Controlled Series Covering a Three-Year Period, Bull. Los Angeles Neurol. Soc. **6**:43 (June) 1943.

4 out of each 5 patients attained full remission by the end of the treatment (three to six weeks). Not more than 10 per cent of this number relapsed. Therapeutic superiority is brought into sharper relief if the controls are limited to the most comparable group, namely, the patients refusing treatment, so that the patients with physical contraindications and those with a condition too mild for treatment are eliminated; the results are then full remission for 90 per cent of the treated patients and for 50 per cent of the untreated patients.

2. More remissions took place with treatment than would otherwise have occurred. For the spontaneous course of the illness is to be considered an important therapeutic contribution. Of the total of 20 deaths, 13 in the control series (9 suicides and 4 deaths from exhaustion) and 3 in the treated series (1 suicide and 2 deaths during treatment), were due to the illness or to the treatment. The 2 patients who died during treatment had abnormalities of the electrocardiogram. One died during the first treatment, and necropsy revealed coronary sclerosis. The second died suddenly twenty-four hours after the second treatment, with no apparent symptoms in the interim.

We wish to emphasize that were it not for the fact that a greater number of untreated

TABLE 2.—*Results of Convulsive Therapy in Patients with Affective Psychoses as Compared with Status of Controls*

	At End of Treatment: Treated Patients		Follow-Up Observations: Outcome of Observed Attacks: Treated Patients		Follow-Up Observations: Outcome of Observed Attacks: Untreated Patients		Follow-Up Observations: Present Status: Treated Patients		Follow-Up Observations: Present Status: Untreated Patients	
	Number	Percentage	Number	Percentage	Number	Percentage	Number	Percentage	Number	Percentage
Remission	69	78	79	90	82	75	71	82	68	62
Improvement	16	18	4	5	6	5	4	7	9	8
No improvement	1	1	2	2	8	8	6	7	15	15
Death	2	3	3	3	13	12	4	4	16	15
	88	100	88	100	109	100	85	100	108	100

TABLE 3.—*Results of Convulsive Therapy for Three Types of Affective Psychoses* *

	Treated Patients: Immediate Results			Treated Patients: Follow-Up Results †				Untreated Patients: Follow-Up Results			
	R	I	U	R	I	U	Total	R	I	U	Total
Manic-depressive depression (136)	75% 40	21% 11	4% 2	85% 45	4% 2	11% 6	100% 53	65% 55	9% 8	26% 20	100% 83
Manic-depressive mania (20)	86% 12	14% 2	....	86% 12	7% 1	7% 1	100% 14	67% 4	....	33% 2	100% 6
Involutional melancholia (39)	77% 17	18% 4	5% 1	81% 18	5% 1	14% 3	100% 22	57% 9	7% 1	36% 7	100% 17

* R indicates recovery; I, improvement, and U, no improvement.
† Under "follow-up results" the outcome is recorded for the original attack under observation; i. e., the effect on recurrent attacks is ignored.

197 patients included, the outcome of the individual attacks under observation was as follows: full remission and improvement in 95 per cent of all treated patients and in but 80 per cent of the untreated patients.[2] These differences are found to be statistically significant (beyond the 1 per cent level on the basis of the chi square test).

3. The treatment prevents death from suicide and exhaustion. This prevention by treatment of deaths which would otherwise take place in patients die when not given the benefits of convulsive therapy, the illnesses of both the treated and the untreated patients would ultimately go on to the same type of outcome.

This is apparent for our earlier patients (metrazol-treated series and controls), for whom the follow-up period was longest, permitting the largest number of controls to show spontaneous remissions. These patients, all seen in the first three years of the period of study, had a follow-up period ranging from thirty to sixty-nine months, with an average of four and a third years, and the illness of 90 per cent of them, treated and untreated alike, has run its course. For these patients, if the deaths are excluded, the incidence

2. The results for the patients treated with electrical convulsions (30) were similar to those of the metrazol-treated series (58) and hence were not separated in this study.

of full remissions is 88 and 86 per cent for treated and untreated patients respectively.[3]

4. No essential difference was observed in the therapeutic results for the subtypes of manic-depressive mania, manic-depressive depression and involutional melancholia[4] (table 3).

5. Relapses which followed either immediately or shortly after the termination of treatment arose chiefly from the same factors as those which contributed to therapeutic failure, namely, incomplete treatment, subconvulsive reactions and advanced age (over 60) (table 4). It is desirable to reserve judgment as to the degree of therapeutic improvement until five weeks after the last treatment, since relapses occur rarely, if at all, if full remission has been maintained for five weeks. Failure to follow this routine in our earlier cases was probably responsible for a number of "relapses" in patients whom we should otherwise not have considered fully recovered. The rate of relapse for patients with the disease in full remission should be less than 10 per cent.

6. Recurrences or new attacks of illness were of equal frequency for both the control and the treated series. Fifteen patients, or 18 per cent, of the treated series had recurrence of attacks, as compared with 24 patients, or 21 per cent, of the untreated series. These figures indicate what many observers have already anticipated, namely, that the beneficial effect of treatment is limited to the individual attack and has no bearing on recurrences.

Perusal of the forty-seven statistical reports[5] in the literature appearing since the publication

TABLE 4.—*Analysis of Data on Twenty Patients with Relapses* *

	Relapses		Without Relapse		Total	
	No.	%	No.	%	No.	%
Total number of patients..	20	100	68	100	88	100
Patients with one or more subconvulsive reactions..	17	85	33	49	50	59
Patients with incomplete treatment.....	19	95	12	18	31	35
Patients over 60 years of age.....	6	30	4	6	10	9
Patients over 50 years of age.....	9	45	22	34	31	36

* The immediate results of treatment were as follows: remissions, 8 patients; improvement, 11 patients; no improvement, 1 patient. The follow-up results were as follows: remissions, 12 patients; improvement, 4 patients; no improvement, 4 patients.

TABLE 5.—*Analysis of Data on Fifteen Patients with Recurrences* *

	Patients With Recurrence		Patients Without Recurrence		Total	
	No.	%	No.	%	No.	%
Total number of patients..	15	100	73	100	88	100
Patients with one or more subconvulsive reactions..	11	74	39	53	50	59
Patients with incomplete treatment.....	8	53	23	31	31	35
Patients with relapse after treatment.....	2	13	18	25	20	18
Patients over 60 years of age.....	2	13	4	6	10	9
Patients over 50 years of age.....	5	33	23	34	32	36

* The immediate results of treatment were as follows: remissions, 13 patients; improvement, 2 patients; no improvement, none.

3. Allowance must perhaps be made in this connection for the fact that the study is loaded in favor of the controls, since the control series contained many more patients with mild disease than did the treated series, conditions too mild to warrant convulsive therapy. A trend toward equalization in outcome is, however, definitely indicated.

4. Only the patients with involutional states were included for whom depression was the outstanding symptom. Patients with paranoid states, patients with schizophrenic-like symptoms or patients with conditions otherwise atypical were excluded, since we believe that insulin shock therapy is the treatment of choice for these patients.

5. (*a*) Barbato, L.: Three Years' Experience with Metrazol Convulsive Therapy (Result and Follow-Up Studies in One Hundred and Sixty-Seven Cases), Dis. Nerv. System **3**:250 (Aug.) 1942. (*b*) Batt, J. C.: One Hundred Depressive Psychoses Treated with Electrically Induced Convulsions, J. Ment. Sc. **89**:289, 1943. (*c*) Bennett, A. E.: Convulsive Therapy: Present Status, Rev. mex. psiquiat., neurol. y med. leg. **9**:23 (July 1) 1942. (*d*) Bianchi, J. A., and Chiavello, C. J.: Shock Therapy in the Involutional and Manic-Depressive Psychoses, Psychiatric Quart. **18**:118 (Jan.) 1944. (*e*) Bieringer, G. S.: Electric Convulsive Therapy, Delaware State M. J. **14**:112 (May) 1942. (*f*) Birch, H. M.: Electric Convulsive Therapy, M. J. Australia **1**:675 (June 20) 1942. (*g*) Cash, P. T., and Hoekstra, C. S.: Electric Convulsive Shock Therapy: Preliminary Curarization (to Eliminate Trauma), Psychiatric Quart. **17**: 20 (Jan.) 1943. (*h*) Cheney, C.; Hamilton, D., and Heaver, W.: Metrazol as an Adjunct to the Treatment of Mental Disorders, ibid. **15**:205 (April) 1941. (*i*) Cleckley, H., and Beard, B.: Electric Shock Therapy in Personality Disorders, J. M. A. Georgia **31**:303 (Aug.) 1942. (*j*) Cummins, J. A.: Experience with 3,057 Administrations of Curare to 202 Psychotic Patients Treated wtih Metrazol, Psychiatric Quart. **17**: 655 (Oct.) 1943. (*k*) Dehne, T. L., and others: Symposium: Complications of and Contraindications to Electric Shock, Arch. Neurol. & Psychiat. **49**:786 (May) 1943. (*l*) Epstein, J.: Electric Shock: Study of One Hundred Cases, J. Nerv. & Ment. Dis. **98**:115 (Aug.) 1943. (*m*) Evans, V. L.: Convulsive (Metrazol and Electric) Shock Therapy in Elderly Patients: Risks and Results, Am. J. Psychiat. **99**:531 (Jan.) 1943. (*n*) Fetterman, J. L.: Electrocoma, Ann. Int. Med. **17**:775 (Nov.) 1942. (*o*) Fitzgerald, O. W. S.: Treatment of Depressive States by Electrically Induced Convulsions, J. Ment. Sc. **89**:73 (Jan.) 1943. (*p*) Furst, W., and Stouffer, J. E.: Electric Shock, J. Nerv. & Ment. Dis. **96**:499 (Nov.) 1942. (*q*) Glueck, B. C., Jr.: Electric Shock Therapy and Psychopathologic Reactions, New York State J. Med. **42**:1553 (Aug. 15) 1942. (*r*) Golden, L. A.: The Treatment of Various Depressive States by Electric Shock (Analyses of 133 Convulsive Cases), Dis. Nerv. System **4**:306 (Oct.) 1943. (*s*) Gonda, V. E.: Treatment of Mental Disorders with Electrically Induced Convulsions, ibid. **2**:

(Footnote continued on next page)

of our last study shows immediate responses to treatment similar to our own. Analysis of 2,777 cases from the same source reveals remissions and notable improvement in 69 per cent, improvement in 18 per cent and no improvement in 13 per cent. Of interest is the remission rate of 56 per cent for the patients with the manic type, as contrasted with a rate of 71 per cent for patients with the manic-depressive depression and of 67 per cent for the patients with involutional melancholia. Our own experience does not bear out the lesser effectiveness of convulsive therapy for the manic type reported in the literature. In our series the results were as good for the manic type as they were for patients with the depressive type. Control studies and long follow-up reports are essentially lacking, so that little has been recorded with respect to the incidence of relapses and recurrences and whether or not the treatment increases the ultimate number of recoveries.

84 (March) 1941. (*t*) Hauser, A., and Barbato, L.: Electric Shock: Preliminary Report, Texas State J. Med. **37**:228 (July) 1941. (*u*) Hemphill, R. E., and Walter, W. G.: The Treatment of Mental Disorders by Electrically Induced Convulsions, J. Ment. Sc. **87**: 256 (April) 1941. (*v*) Impastato, D. J., and Almansi, R.: Electrofit, J. Nerv. & Ment. Dis. **96**:395 (Oct.) 1942. (*w*) Kalinowsky, L.; Bigelow, N., and Brikates, P.: Electric Shock Therapy in State Hospital Practice, Psychiatric Quart. **15**:450 (July) 1941. (*x*) Kay, F. A.; Smith, J. D., and Reim, N. H.: Electroshock Treatment in Psychiatric Disorders, J. M. A. Alabama **12**:129 (Nov.) 1942. (*y*) Kennedy, F., and Wiesel, B.: Report on Results of Electric Shock Treatment on Mental and Emotional Symptoms, New York State J. Med. **42**:1663 (Sept. 1) 1942. (*z*) Kepner, R. D.: Metrazol Therapy of Psychoses: Evaluation; Comparative Analysis of 152 Treated Cases, M. Rec. **154**: 423 (Dec. 3) 1941. (*a'*) Levy, N. A.; Serota, R. M., and Grinker, R. R.: Disturbances in Brain Function Following Convulsive (Metrazol and Electric) Shock Therapy: Electroencephalographic and Clinical Studies, Arch. Neurol. & Psychiat. **47**:1009 (June) 1942. (*b'*) Malzberg, B.: Electric Shock Therapy: Outcome in New York Civil State Hospitals, Psychiatric Quart. **17**:154 (Jan.) 1943. (*c'*) Myerson, A.: Electric Shock, New England J. Med. **224**:1081 (June 26) 1941; (*d'*) Further Experience with Electric-Shock Therapy in Mental Disease, ibid. **227**:403 (Sept. 10) 1942. (*e'*) Nielsen, J. C.; Geshell, S. W., and Coen, R. A.: Review of Pharmacologic Shock Therapy (Insulin Picrotoxin and Metrazol) at Hastings State Hospital, Dis. Nerv. System **3**:122 (April) 1942. (*f'*) Pacella, B. L., and Barrera, S. E.: Follow-Up Study of Series of Patients Treated by Electrically Induced Convulsions and by Metrazol Convulsions, Am. J. Psychiat. **99**:513 (Jan.) 1943. (*g'*) Petersen, M. C., and Turner, T. R.: Electric Convulsive Therapy, M. Clin. North America **27**:1019 (July) 1943. (*h'*) Prosser, J. P.: Shock Therapy (Especially Metrazol) in Affective Disorders, J. Oklahoma M. A. **34**:471 (Nov.) 1941. (*i'*) Rennie, T. A. C.: Shock Therapy: Present Status, Psychiatry **6**:127 (May) 1943; (*j'*) Prognosis in Manic-Depressive and Schizophrenic Conditions Following Shock Treatment, Psychiatric Quart. **17**:642 (Oct.) 1943. (*k'*) Reznikoff, L.: Electric Shock: Indications and Results, ibid. **17**:355 (April) 1943. (*l'*) Rickles, N. K.: Electric Shock Therapy: Report from One Hundred Private Cases, Northwest Med. **43**:44 (Feb.) 1944. (*m'*) Rosen, S. R.; Secunda, L., and Finley, K. H.: The Conservative Approach to the Use of Shock Therapy in Mental Illness, Including Study of Electroencephalograph Tracings Before, During and After Shock Therapy, Psychiatric Quart. **17**:617 (Oct.) 1943. (*n'*) Smith, L. H.; Hughes, J.; Hastings, D. W., and Alpers, B. J.: Electric Shock in Psychoses, Am. J. Psychiat. **98**:558 (Jan.) 1942. (*o'*) Wender, L.; Balser, B. H., and Beres, D.: Extramural Shock Therapy, ibid. **99**:712 (March) 1943. (*p'*) Wilson, D. C.: Treatment of Mental Diseases Related to Involutional Period, Virginia M. Monthly **70**:175 (April) 1943. (*q'*) Woolley, L. F.; Jarvis, J. R., and Ingalls, G. S.: Use of Curare in Modifying Convulsive Shock (Metrazol and Electric), J. Nerv. & Ment. Dis. **96**:680 (Dec.) 1942. (*r'*) Wyllie, A. M.: Electric Convulsion Therapy, Lancet **2**:71 (July 19) 1941. (*s'*) Young, R. H.: Evaluation of Pharmacologic Shock Therapy: Four Years' Experience, J. Omaha Mid-West Clin. Soc. **2**:76 (Aug.) 1941. (*t'*) Zeifert, M.: Metrazol: Results Obtained from Administration of 12,000 Doses; Preliminary Report, Psychiatric Quart. **15**:772 (Oct.) 1941. (*u'*) Zifferstein, L.: Metrazol Convulsive Therapy, J. Iowa M. Soc. **31**:531 (Nov.) 1941.

FACTORS CONTRIBUTING TO THERAPEUTIC FAILURE

Subconvulsive Reactions.—As stated in our previous studies, patients who have no subconvulsive reactions during treatment do considerably better than patients having one or more such reactions (tables 6 and 7). Metrazol-treated patients and patients treated with electric shock are alike in this regard. However, introduction of a modified technic which excluded these nonconvulsive reactions [6] with our last 20 electrically treated patients yielded an improved therapeutic response, namely, full immediate remission in 87 per cent.

TABLE 6.—*Relation of Full Remissions to Incidence of Subconvulsive Reactions*

Incidence of Subconvulsive Reactions, %	Patients with Remissions	
	Number	Percentage
0	34	94
25 or less	27	75
Over 25	8	62

Goldman [7] noted that subconvulsive reactions in electrically treated patients had no deterrent effect, though he stated the belief that they are harmful in metrazol therapy. From data published by Kennedy and Wiesel [5y] and Wender, Balser and Beres, [5o'] it appears that subconvulsive reactions had no harmful

6. Somerfeld-Ziskind, E., and Ziskind, E.: Prevention of Sub-Convulsive Reactions in Convulsive Therapy for Psychoses, J. Nerv. & Ment. Dis. **99**:889 (June) 1944.

7. Goldman, D.: Personal communication to the authors.

effect, though this is difficult to state because such reactions occurred in practically every case. On the other hand, Kennedy [8] stated that "petit mal" reactions were not only useless but actually harmful. Apparently, the harmful effect of subconvulsive reactions is insufficient to prevent remissions in most cases. Our experience suggests, however, that it does contribute to therapeutic failure and relapse.

Inadequate Treatment.—Failure to administer a full course of therapy covering (1) the acute period of the symptoms, (2) one or two reenforcement treatments and (3) additional treatments in the immediate postdischarge period if early signs of relapses appear is responsible for a large number of therapeutic failures. Confusion as to whether persistence of mild symptoms is residual from the illness or arises as an effect of treatment often makes it difficult to determine whether or not treatment should be continued. The five week post-treatment period of observation is therefore important in this connection.

Age.—Analysis of the results in patients over and under 60 and 50 years of age respectively (table 8) shows a higher rate of recovery for the younger patients. For instance, the immediate rate of recovery for patients under 50 years is 81 per cent, as compared with only 62 per cent for patients over 50 years and 56 per cent for patients over 60 years of age. Similar results were obtained by Fitzgerald.[5o] Evans,[5m] although not reporting on the younger age groups, recorded a full remission rate of only 50 per cent for patients over 50 years of age. Cash and Hoekstra [5g] obtained better results with patients above than with patients below 50 years of age.

TABLE 7.—*Effect of Subconvulsive Reactions on Results of Treatment* *

Number of Subconvulsive Reactions	Total	Immediate Results			Follow-Up Results †				
		R	I	U	R	I	U	Relapses	Recurrences
None	41% 36	94% 34	6% 2	.. ..	94% 34	.. ..	6% 2	4% 3	11% 4
One or more	59% 50	70% 35	28% 14	2% 1	86% 43	6% 3	8% 4	34% 17	22% 11

* R indicates recovery; I, improvement, and U, no improvement.
† Follow-up results according to the outcome of the treated attack.

TABLE 8.—*Results of Treatment in Relation to Age*

Age Group	Total Group Distribution of Patients According to Age (Percentage)		Full Remissions (Percentage)			No Improvement (Percentage)	
			Immediate Results:	Follow-Up Results		Follow-Up Results	
	Treated Patients	Controls	Treated Patients	Treated Patients	Controls	Treated Patients	Controls
Cumulative Percentage of Patients up to Age of 70 Years							
Under 50	64	67	81	98	90	1	4
Under 60	89	83	75	93	84	6	9
Under 70	99	96	74	89	80	7	14
Cumulative Percentage of Patients Over Age of 50 Years							
60 and over	10	13	56	56	43	22	50
50 and over	35	29	62	77	52	16	36

HAZARDS OF THERAPY

The unknown quantity, damage to the brain, still remains the major consideration referable to the dangers of treatment. Reports on the working ability of our recovered patients reveal, however, that it is as good as, or even better than, it was in the prepsychotic period. One gains the impression, therefore, that there cannot be any serious impairment to the brain, the reports of their performance being as good as they are. Despite many subjective factors, these clinical impressions are in our opinion as significant as interpretations arising secondarily from laboratory procedures, such as psychologic tests and electroencephalographic records.

SUMMARY

1. For the 88 treated patients the immediate results were as follows: full remission, 78 per cent; improvement, 18 per cent, and no improvement, 4 per cent. The period of treatment was three to six weeks.

2. The follow-up results for these patients, as compared with the results for an untreated

8. Kennedy, P.: Round-Table Discussion on Electric Shock Therapy, read at a meeting of the American Psychiatric Association, 1943.

control group were as follows: full remission in 90 per cent of the treated patients and in only 75 per cent of the untreated patients.

3. In the series of untreated patients there were 9 deaths from suicide and 4 deaths from exhaustion, as compared with 1 death from suicide in the series of treated patients. Two patients with heart disease died during treatment.

4. The incidences of ultimate full remission for our patients with the longest period of follow-up observation (from June 1938 to June 1941) were the same (88 and 86 per cent) for treated and for untreated patients respectively, provided the deaths were omitted from each series.

5. The therapeutic results were the same for all subtypes of affective psychoses: manic-depressive mania or manic-depressive depression and involutional melancholia.

6. Twenty patients had relapses. Of this group, only 8 were classified as having full (?) remissions. Eighty-five per cent of the patients who had relapses had one or more nonconvulsive reactions during treatment.

7. Recurrences (new attacks) occurred with equal frequency in the control and in the treated series, the percentages being 21 and 18 respectively.

8. Full remissions occurred in 94, 75 and 62 per cent of patients having no, one or more and over 25 per cent of subconvulsive reactions respectively.

9. The immediate rate of recovery for treated patients more than 60 years of age was 56 per cent, as compared with the rate of 75 per cent for patients under 60.

10. Working ability after recovery by treatment was as good as and better than prior to the illness. No cerebral damage from the treatment was apparent as judged by the patient's working ability subsequent to treatment.

CONCLUSIONS

1. The benefits of convulsive therapy of the affective psychoses are to be gaged by the reduced period of illness and the greater number of recoveries. The latter effect is due to the decreased number of deaths rather than to any inherent greater therapeutic effect. The treatment in itself is not responsible for any greater incidence of recovery than that which occurs spontaneously if the patient is shielded from death by suicide or exhaustion.

2. The known hazards of treatment for treated patients are less than the hazards for untreated patients. In this study 13 died as a result either of suicide or of exhaustion.

3. Subconvulsive doses, incomplete therapy and old age are unfavorable factors. Subconvulsive reactions should be avoided.

4. The tendency to recurrences or to new attacks is apparently not influenced by treatment.

5. The possibility of damage to the brain still calls for quantitative evaluation. A margin of safety may be found.

6. This study presents an equal number of control (untreated) and treated patients. More such studies are needed in order to solve adequately the problem of the effect of convulsive therapy of the affective psychoses.

2007 Wilshire Boulevard.

CARCINOMA OF THE UTERINE FUNDUS WITH METASTASIS TO THE BRAIN

REPORT OF A CASE

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The purpose of this paper is to report what is believed to be a rare case of carcinoma of the uterine fundus with metastasis to the brain. In a review of the literature, we found several reports mentioning the occurrence of metastatic cerebral lesions from a carcinoma of the uterine fundus. However, in no report are the criteria of diagnosis of this lesion given, and we have found no case in which both the primary and the secondary site were examined grossly and microscopically during life.

INCIDENCE OF METASTATIC TUMORS OF THE BRAIN

Meagher and Eisenhardt,[1] in reviewing 1,850 cases of intracranial neoplasm, found that 57, or 3 per cent, were metastatic. Elkington[2] reported 72 cases of metastatic tumors of the brain in a series of 805 cases of cerebral tumor, an incidence of 9 per cent. Dandy[3] estimated the incidence of metastatic cerebral tumor to be 10 per cent of all varieties of tumors of the brain. Adson,[4] however, noted only 2 cases of metastatic tumor in 167 cases of cerebral neoplasm. Globus and Meltzer[5] reported an incidence of 13.5 per cent in a series of 57 cases. Garland and Armitage,[6] in reporting the results of 264 autopsies in cases of cerebral tumor, stated that 12.8 per cent of the tumors were metastatic. In one third of the series the cerebral lesions arose from tuberculoma. When these granulomatous lesions were excluded, the percentage of metastatic tumors in their series became 17.1 per cent. On the basis of these reports, the incidence of metastatic tumors of the brain varied from 12 to 17.1 per cent.

ORIGIN OF METASTATIC TUMORS OF THE BRAIN

Metastatic tumors of the brain are not an infrequent complication of carcinoma and sarcoma. Krasting,[7] in examining the tissue in 12,730 cases in which autopsy was done, observed malignant disease in 1,238, or 9.18 per cent. In this series there were 1,078 cases of carcinoma and 160 cases of sarcoma. Examination of the brain was possible in 935 of the 1,238 cases. Of these, 817 were cases of carcinoma, in 39, or 4.7 per cent, of which metastasis occurred to the brain. Of the 118 instances of sarcoma in this series of 935 cases, cerebral metastasis had occurred in 14, an incidence of 12.4 per cent. Rau,[8] in a series of 10,393 autopsies, observed that 3.2 per cent of the carcinomas and 68.1 per cent of the sarcomas had metastasized to the brain. Neustaedter,[9] in examining the records of admissions to the New York City Cancer Hospital, noted metastatic carcinoma to the nervous system in 143 of 6,761 cases, an incidence of 2.15 per cent. Certain neoplasms have a predilection to metastasize to the brain. Carcinoma of the lung and breast are the commonest primary sites. Of 139 cases of meta-

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1. Meagher, R., and Eisenhardt, L.: Intracranial Carcinomatous Metastases, Ann. Surg. **93**:132, 1931.

2. Elkington, J. S.: Metastatic Tumours of the Brain, Proc. Roy. Soc. Med. **28**:1080, 1935.

3. Dandy, W. E.: Metastatic Tumors, in Lewis, D.: Practice of Surgery, Hagerstown, Md., W. F. Prior Company, Inc., 1932, vol. 12, p. 669.

4. Adson, A. W.: The Surgical Consideration of Brain Tumors, Quart. Bull., Northwestern Univ. M. School **35**:1, 1934.

5. Globus, J. H., and Meltzer, T.: Metastatic Tumors of the Brain, Arch. Neurol. & Psychiat. **48**:163 (Aug.) 1942.

6. Garland, H. G., and Armitage, G.: Intracranial Tuberculoma, J. Path. & Bact. **37**:461 (Nov.) 1933.

7. Krasting, K.: Beitrag zur Statistik und Kasuistik metastatischer Tumoren, besonders der Carcinommetastasen im Zentralnervensystem, Ztschr. f. Krebsforsch. **4**:315, 1906.

8. Rau, W.: Eine vergleichende Statistik der in 5 Kriegsjahren (1914-1919) und 5 Friedensjahren (1909-1914) sezierten Fälle von Krebs und anderen malignen Tumoren am pathologischen Institut des Stadtkrankenhouses Dresden-Friedrichstadt, Ztschr. f. Krebsforsch. **18**:141, 1921.

9. Neustaedter, M.: Incidence of Metastases to the Nervous System, Arch. Neurol. & Psychiat. **51**:423 (May) 1944.

static cerebral neoplasm, Krasting [7] observed that 40 cases, or 25 per cent, followed mammary carcinoma and 29, or 20 per cent, pulmonary carcinoma. Dosquet [10] noted metastasis to the brain in 31.4 per cent of 105 cases of carcinoma of the lung, and Fried,[11] in 16, or 34 per cent, of his series of 47 cases of similar neoplasms. Handley [12] observed cerebral metastasis in 16, or 5 per cent, of 329 cases of primary malignant growths of the breast. Both Krasting [7] and Bailey [13] stated that 50 per cent of all melanotic sarcomas metastasize to the brain.

Elkington [2] reported 72 cases of metastasis to the brain, with the following distribution of primary sites: breast, 18 per cent; lung, 33.3 per cent; gastrointestinal tract, 9.7 per cent; nasopharynx, 8.3 per cent; kidney, 6.9 per cent; urogenital tract, 12.5 per cent; pigmentary structures, 5.6 per cent; miscellaneous areas, 2.8 per cent, and undetermined site, 2.8 per cent. Meagher and Eisenhardt [1] reported 40 cases, with the primary sites as follows: breast, 25 per cent; lung, 35 per cent; gastrointestinal tract, 15 per cent; nasopharynx, 5 per cent; kidney, 2.5 per cent; urogenital tract, 2.5 per cent, and undetermined site, 25 per cent. Dunlap [14] reported 77 cases, the primary sites being distributed as follows: breast, 15.6 per cent; lung, 11.7 per cent; gastrointestinal tract, 13 per cent; nasopharynx, 2.5 per cent; kidney, 15.6 per cent; urogenital tract, 6.5 per cent; pigmentary structures, 6.5 per cent; miscellaneous sites, 18.3 per cent, and undetermined site, 10.3 per cent. In 1 case the cerebral metastasis was reported as primary in the uterus. However, neither the primary nor the secondary site was examined grossly or microscopically to confirm the diagnosis. Neustaedter [9] found 52 cases of malignant metastasis to the brain and reported the primary sites as follows: breast, 27 per cent; lung, 15.4 per cent; nasopharynx, 30.8 per cent; uterus, 5.8 per cent; rectum, 4 per cent; skin, 4 per cent; bladder, 2 per cent; hard palate, 2 per cent; antrum, 2 per cent, and tongue, 7 per cent. This author did not give his criteria for diagnosis of the 3 cases of primary uterine carcinoma with metastasis to the brain, no mention being made as to whether the diagnosis was presumptive or was verified by biopsy, operation or autopsy.

In a review of the literature of secondary metastatic tumors of the brain, we have found the reported incidence of metastatic cerebral tumor with the primary site in the uterus to be low. In the reported cases of these cerebral tumors, no criterion, such as pathologic examination of the primary and secondary sites, either at operation or at autopsy, is given. In the case to be reported the patient had an adenocarcinoma of the fundus of the uterus (fig. 1 *A* and *B*). A total hysterectomy was done, and several months later signs and symptoms of a cerebral neoplasm developed. At operation a metastatic tumor was observed, the sections of which were identical with the sections taken from the uterus (fig. 2 *A* and *B*).

REPORT OF CASE

F. M. M., a white woman aged 48, was admitted to the hospital with a complaint of weakness in the right leg, of nine months' duration, and twitching of the musculature of the right leg, of five months' duration. The family history was noncontributory. The personal history revealed that twenty-two months prior to admission she began to have uterine bleeding, which was diagnosed by her local physician as functional. She was given radium therapy. Thirteen months before admission she began to experience dull pain in the lower part of the abdomen, with radiation to both hips, and had urinary frequency and nocturia. Three months later she became aware of weakness in the right leg. Six months before admission her local physician performed a panhysterectomy. The specimen was sent to this hospital for pathologic examination and was diagnosed as adenocarcinoma of the uterine fundus. Postoperative convalescence was uneventful for two weeks, when she began to have twitching in the right leg, which lasted four to five minutes at a time and was followed by notable weakness of this extremity. Such attacks came on with increasing frequency and severity. Weakness was progressive, and the patient noted that she dragged her right foot while walking. Two weeks before admission to the hospital she had a convulsive seizure, characterized by twitchings in the right foot, which developed into clonic contractions and spread up the right side of the body to involve the right arm and then became generalized, with loss of consciousness. After this attack she experienced a severe generalized headache and numbness of the left side of the face, the right arm and the right leg. Since that time she had had a mild generalized headache, with no nausea or vomiting. There were no visual disturbances or other neurologic symptoms.

Examination revealed normal temperature, pulse and respiration, with a blood pressure of 150 systolic and 100 diastolic. Results of general physical examination were not remarkable. The positive features of the neurologic examination were slight atrophy and spasticity of the musculature of the right calf. The patient

10. Dosquet: Ueber die Metastasenbildung bei primären Lungen-und Bronchialkrebsen, Virchows Arch. f. path. Anat. **234**:481, 1921.

11. Fried, B. M.: Primary Carcinoma of the Lung, Baltimore, Williams & Wilkins Company, 1932, p. 125.

12. Handley, W. S.: Cancer of the Breast, ed. 2, New York, Paul B. Hoeber, 1922, p. 160.

13. Bailey, P.: Intracranial Tumors, Springfield, Ill., Charles C Thomas, Publisher, 1933.

14. Dunlap, H. F.: Metastatic Malignant Tumors of Brain, Ann. Int. Med. **5**:1274 (April) 1932.

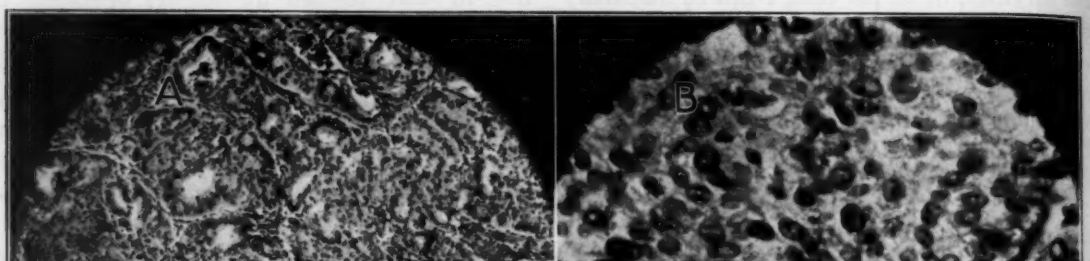

Fig. 1.—Field at left (*A*), × 112; field at right (*B*), × 684. Section of the uterine fundus, showing typical adenocarcinoma. Numerous enlarged and elongated alveoli are lined with several layers of compact cuboidal and cylindric cells, the bodies of which are pale. The nuclei are large and hyperchromatic, and mitoses are seen throughout the section. In several areas there are sheets of disorganized tumor cells, with little tendency to gland formation.

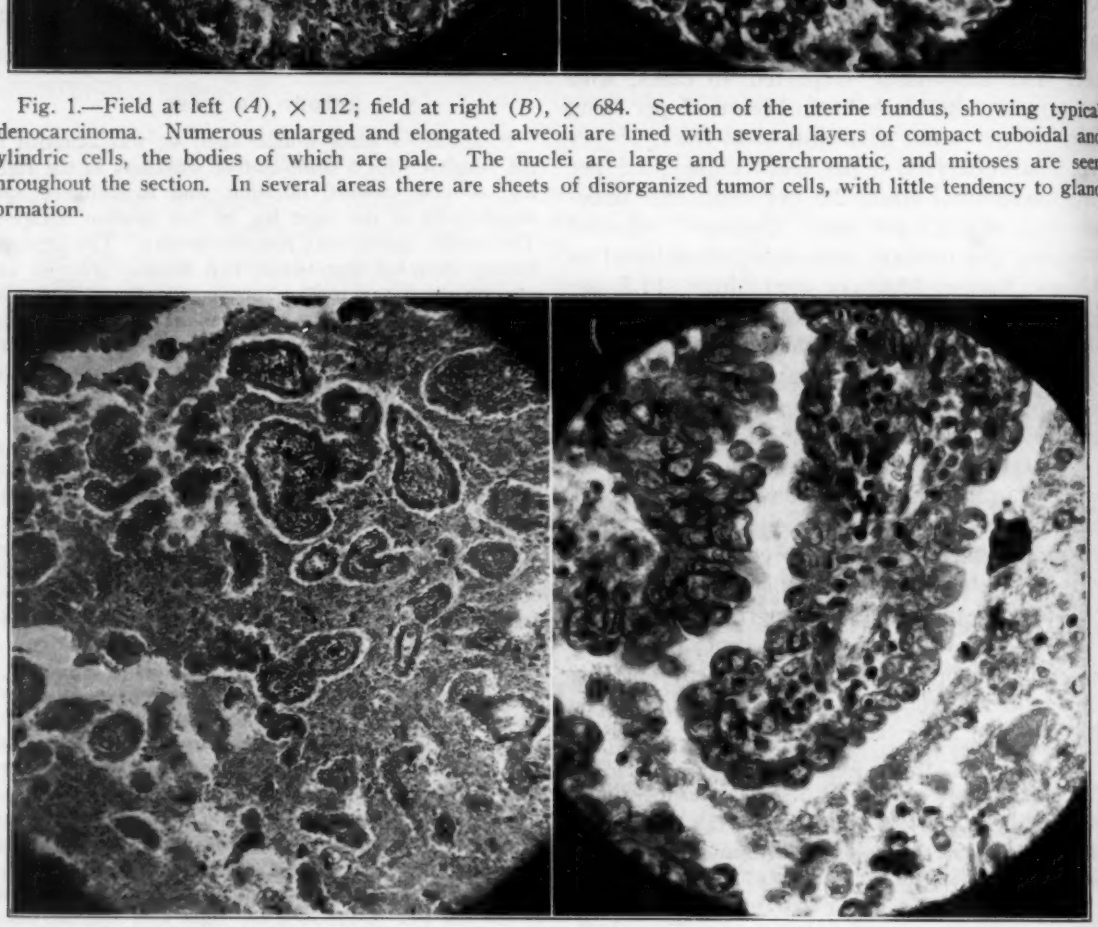

Fig. 2.—Field at left, × 112; field at right, × 684. Section of the brain, showing numerous large tumor cells which are cuboidal and cylindric. The nuclei are large and hyperchromatic, and occasional mitoses are seen. Glandular and papillary formations are striking features. However, some of the cells are scattered in diffuse sheets and cords. In all sections the tumor is infiltrating the brain substance. This tumor is an adenocarcinoma metastatic from the uterine fundus and is similar to the primary uterine carcinoma seen in figure 1 *A* and *B*.

was unable to dorsiflex or to evert the foot. There was also slight spasticity of the muscles of the thigh. Papilledema was not present, and the cranial nerves were not involved. The reflexes on the right side were slightly hypoactive; the abdominal reflexes were absent, and the plantar reflexes were equivocal. Serologic reactions for syphilis gave negative results. The impression was that this patient had a metastatic lesion from the carcinoma of the fundus of the uterus. However, the possibility of a primary cerebral neoplasm could not be ruled out. On her sixth day in the hospital bilateral posterior trephinations, with ventriculographic study, were made; they disclosed flattening of the left lateral ventricle in its midportion, with slight dislocation of the ventricular system to the left, suggestive of a parasagittal tumor on the left side. Dr. Barnes Woodhall performed a craniotomy and exposed a nodular tumor, lying about 2 cm. below the surface of the hemisphere along the midline. The mass was about 4 cm. in diameter and certainly could not have caused the extreme cerebral edema which was present. The tumor was gently dissected until its periphery was quite clear and it was easily shelled out of the brain tissue. However, it was not well circumscribed and did not represent a meningioma, but seemed to infiltrate the brain tissue mesially; on section its appearance immediately suggested a metastatic lesion. No other metastases could be seen or palpated, although it was felt there was a pronounced sense of resistance deep in the white matter toward the ventricle. This tumor involved the motor and sensory cortex on the left side, and pathologic study revealed an adenocarcinoma, the miscroscopic picture being identical with that of the tumor of the uterine fundus. This patient was followed for the two years before her death; at no time did she show any evidence of metastasis other than to the brain.

SUMMARY AND CONCLUSIONS

A patient aged 48, six months previous to admission to the hospital, had undergone a panhysterectomy for an adenocarcinoma of the fundus of the uterus. Two weeks after the operation she began to have twitching, atrophy, slight spasticity and weakness of the right lower extremity, the symptoms being progressive. Two weeks before she was seen at this hospital, a generalized convulsive seizure developed, the onset being focal in character; the convulsion started in the right foot and extended up the right leg, involved the right arm and then passed into the generalized phase. The preoperative diagnosis was probable metastatic tumor to the brain. However, the possibility of a primary tumor could not be ruled out. At operation the patient was observed to have a metastatic tumor to the brain, the pathologic section being identical with that of the uterine carcinoma. We have been unable to find the report of any authenticated case in which uterine carcinoma metastasized to the brain with pathologic examination of the primary and secondary sites during life. There are reports giving the incidence of metastasis of uterine carcinoma to the brain, but no conclusive criteria for that diagnosis were established, as was done in this case.

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CAUSALGIA

REPORT OF RECOVERY FOLLOWING RELIEF OF EMOTIONAL STRESS

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Although it has been apparent that many persons who suffered from causalgia were emotionally unstable, it has seemed doubtful that localized and unilateral autonomic dysfunctions could depend on emotional factors. The case which is reported is of interest in that the full blown syndrome cleared rapidly when the patient was relieved of his emotional distress.

The term causalgia is used to designate a condition, or a group of closely related syndromes, which has received a large number of names.[1] The condition follows injury to an extremity. It is characterized by intense burning pain, which is aggravated into severe paroxysms by trivial physical and emotional stimuli. The skin of the area involved is extremely hyperalgesic, and the slightest movement is painful. These complaints are accompanied by tangible evidence of localized autonomic dysfunction. The skin is red or blue, hot or cold, the state perhaps depending on the duration of the condition, and it may show trophic changes in its texture. The region is wet with perspiration, in contrast to the opposite, normal extremity. There is edema, which may extend into the joint. The muscles are taut, splinting against motion, and there is apt to be muscular wasting. After the condition has persisted for a number of weeks, there may be roentgenographic evidence of osteoporosis, which is greater than would be anticipated from disuse. The pain and hyperalgesia are likely to spread beyond the original limits and in cases of severe form involving the hand may extend into the arm and, finally, into the shoulder girdle. Cases of the late stage tend to be intractable to all forms of treatment, including cervical chordotomy, though medullary tractotomy may be efficacious. The sufferer may become addicted to opiates, may end in an institution for mental disease or may commit suicide.

Causalgia may complicate any one of a wide variety of trauma to an extremity; injuries to the brachial plexus, particularly gunshot wounds; partial lesions of the large nerves; arterial or venous occlusions; fractures; sprains; infected wounds, and, at times, trivial bruises or other minor injuries. It appears certain that a hematoma of the nerve sheath or an arterial occlusion may set up a reflex vasospasm that brings on the chain of symptoms. It is not clear why some simple injuries are followed by causalgia. It has been noted that the condition is likely to occur in persons who had shown previous indications of unstable vasomotor reactivity,[1c] and it has been remarked that some of the patients are unstable emotionally. It is often obscure by the time the patient is studied whether the instability preceded the injury or followed the prolonged suffering.

The nature of the physiologic changes which produce the disability has not been fully clarified. There is agreement concerning the obvious fact that there is localized autonomic dysfunction which causes vasomotor abnormalities. Most investigators consider the phenomena to be secondary to reflex vasospasm induced by stimuli originating in the vessels, nerve trunks or nerve endings in joints. There is evidence, however, that vasodilatation, with distention of the capillaries, and arteriovenous shunts[1b] may play a responsible role. Both vasospastic and vasodilator mechanisms have been invoked to explain the signs shown by the same patient.[1d] The neurophysiologic concepts have been reviewed by Miller and de Takáts.[1a]

A variety of treatments have been advocated.[1] Because of the intractability of the late stage, there is agreement that the abnormal pattern of reflexes must be interrupted as soon as possible. The mild form is said to respond to immobilization, physical therapy and reassurance. Attention is paid to whatever injury or infection exists, and excision of a thrombosed vessel or removal of an organizing hematoma of a nerve sheath may bring immediate relief. Local injections of procaine hydrochloride may be of benefit. Injec-

* Major Lidz is on leave of absence from the Henry Phipps Psychiatric Clinic.

1. (*a*) Miller, D. S., and de Takáts, G.: Post Traumatic Dystrophy of the Extremities, Surg., Gynec. & Obst. **75**:558 (Nov.) 1942. (*b*) de Takáts, G.: Nature of Painful Vasodilatation in Causalgic States, Arch. Neurol. & Psychiat. **50**:318 (Sept.) 1943. (*c*) White, J. C., and Smithwick, R. H.: The Autonomic Nervous System, ed. 2, New York, The Macmillan Company, 1941. (*d*) Homans, J.: Circulatory Diseases of the Extremities, ibid., 1939.

tions of procaine into the sympathetic ganglia may produce permanent or temporary cessation of symptoms; when only temporary benefit is gained, some form of surgical interruption of the sympathetic fibers is indicated. Long-standing conditions, as has been mentioned, may not be benefited by such procedures.

Attention has been called to the importance of emotional factors. Miller and de Takáts [1a] stressed the importance of "alleviation of fear, anxiety, and reassurance of the patient and avoidance of all factors which may lead to a conscious or unconscious prolongation of a painful syndrome." They stated, however, that "there is no clear-cut evidence that the post traumatic emotional status of a patient can actually influence the local autonomic reflexes originating from an injury." It is with this in mind that the following case is reported.

REPORT OF A CASE

A 20 year old private, with eight months of Army service, was admitted to a general hospital in the South Pacific on Jan. 19, 1944, by transfer from an evacuation hospital. On Dec. 23, 1943, while in a noncombat area, he had wounded himself while cleaning his rifle. His right hand had been over the muzzle when the gun discharged. The bullet shattered the proximal phalanx of the middle finger and caused a compound fracture of the fourth metacarpal and a laceration extending along the proximal portion of the ring finger. The wound had been treated by débridement and the middle finger disarticulated and amputated at the metacarpophalangeal joint. The hand had been kept in plaster for three weeks, and the discomfort and pain suffered were not disproportionate to the injury. After removal of the cast the soldier sometimes complained of pain. On one occasion he sought relief by wrapping his hand about a light bulb. This caused intense pain, unlike anything he had experienced before, but it subsided within a few minutes. He was transferred to the general hospital because contracture of the ring finger necessitated prolonged hospitalization. On arrival at the general hospital, twenty-nine days after the injury, the wound was healing well. The contracture was moderate, and there was little complaint of pain, even with motion. The past history was noncontributory except that he had injured his right shoulder at the age of 16, apparently without fracture. This accident had not been accompanied by symptoms referable to the distal portion of the extremity. Physical examination revealed slight winging of the right scapula and slight limitation of abduction of the arm. No other physical abnormalities were found. The results of routine laboratory tests were all normal.

The hand was treated with progressive exercises, and the wound was handled conservatively. The range of motion in the ring finger increased slowly but steadily, and the wound healed well. Forty-nine days after the injury, when the wound was completely healed, heat treatment was started. During the first treatment, while he was holding the hand under the heat lamp, the soldier again experienced intense pain in the entire hand, which persisted as moderate pain for twenty-four hours. A second treatment on the following day made the pain still worse. The patient's condition altered notably. He complained of constant and intense burning pain in the entire hand, which was intensified greatly by the slightest touch or by movement of any of the fingers. The range of motion in the ring finger diminished, and he became reluctant to move any of the fingers, all of which he held in flexion. The condition continued to grow worse. The hand became flushed and edematous and was always wet with perspiration. The edema spread to involve the entire hand distal to the carpus. The patient suffered severely and slept little, despite sedation. Salicylates and codeine afforded little relief.

For ten days after the onset of the severe pain the condition continued to grow worse. The soldier was reexamined carefully. The blood pressure was 140 systolic and 100 diastolic in both arms, but, aside from the winging of the scapula, the significant findings were otherwise limited to the right arm. Pressure over the right brachial plexus was slightly painful, in contrast to the effect on the left side. Further tests for the scalenus anticus syndrome gave negative results. There was slight atrophy of the muscles of the right upper extremity, including the biceps and the muscles of the forearm, but not more than was to be anticipated from disuse. The wounds of the hand were well healed. There were a few scaled areas on the palm, residue of small "blisters," which appeared to be trophic manifestations. The contrast between the two hands was striking. The left hand appeared normal in contour, color, temperature, moistness and range of motion. The right hand was deeply flushed, wet and cool, and the entire hand, particularly the palm, was edematous. The fingers, aside from the thumb, were held in pronounced flexion. All movements were excruciatingly painful, and only after strong persuasive suggestion was it learned that the fingers could be moved and that strength was good in all except the ring finger. The skin of the hand, especially the palmar surface, was hypersensitive to light touch. The area distal to the wound on the ring finger was hypesthetic.

The diagnosis of causalgia was made, and injections of procaine into the first and second thoracic sympathetic ganglia were considered as a preliminary measure. However, as the patient had shown notable alteration in his behavior after the onset of the pain, and had become moody and ceased to participate in ward activities, psychiatric opinion was sought before active measures were taken.

The patient was seen in psychiatric consultation eleven days after the onset of the severe pain. He appeared worn, moderately depressed and on edge. He was alert and cooperative, and there were no indications of psychotic trends. He complained of being tired, owing to loss of sleep and the constant pain. There were no complaints other than those associated with the hand. His history prior to induction was essentially noncontributory. His parents were living and were in excellent health. His home had been congenial. There had been no neurotic traits in childhood or adolescence, and there were no indications of emotional instability. He had always been congenial and outgoing and had made friends readily. Grade school had been completed without faliures. The patient had then worked on a ranch and had been enthusiastic about training horses. He had married the daughter of the ranch owner a year before his induction and had enjoyed a happy married life. He recalled that after his injury, at the age of 16, when he had fallen from a horse, he had been apprehensive of training horses for a short time but had overcome his fears and had begun to compete in rodeos as a hobby.

The interview soon centered on the origin of the wound and the patient's reaction to it. He stated that he had turned in his rifle when hospitalized with dengue, and the accident had occurred on the day of his release from the hospital. He had given no thought to the possibility that his rifle might be loaded when he had

drawn it from the supply room, as he had never loaded it at any time. He had been wiping the barrel with a rag when he hit the trigger and the gun discharged. When further questions were asked, the soldier started to cry. Ever since he had been interviewed by the psychiatrist at the evacuation hospital, he had realized that it was suspected that he had maimed himself to avoid combat. His unit had been alerted to leave for combat while he had been in the hospital with dengue. The patient was a replacement in a unit that had experienced considerable jungle fighting; after hearing the tales, he had felt somewhat apprehensive, but he denied vehemently having entertained thoughts of injuring himself to avoid fighting. He had not seriously considered the implications that others would place on his injury until some time after his arrival at this hospital, when he had been informed by the ward officer that a line of duty board had found that the injury had not been incurred in the line of duty. He had then become severely upset, as he assumed that it was held that he had shot himself purposefully. He started to worry about what his friends in his company thought of him and what his family would think. He feared that he would be discharged dishonorably from the Army and that his wife would wish a divorce and his parents would not care to have him about their home. He felt that if the line of duty board had found this injury to be wilful, others would form the same opinion. He had considered an appeal but realized that appearances and the testimony were against him. He had tried to cover his feelings but had difficulty in keeping himself from crying, and much of each night was spent in worrying about the situation. The patient was certain that he had been told of the findings of the board on the day before the onset of the acute pain and had slept little that night.

The testimony was injurious to the patient. Circumstantially, it was difficult to see how there could have been a bullet in the rifle unless he had placed it there. Nevertheless, the investigating authority had been impressed, as the psychiatrist at the evacuation hospital had been, with the soldier's sincerity and had found that the wound had been purely accidental. However, a superior authority had reversed the decision after reading the testimony and had found that the injury had not been incurred in the line of duty. It was this reversal of the decision of which the soldier had learned on the day prior to the onset of the causalgia.

The situation was discussed with the patient. It was explained that an investigation by the line of duty board is not a court-martial. It had not been recommended that he be tried by court-martial, which would have been the case if it had been thought that he had wounded himself wilfully. The implications of the decision of the board were not minimized, but his attitude toward it, particularly his hopelessness and resentment, was discussed. It was a situation which, even if he considered it a miscarriage of justice, was understandable and must be met. Considerable discussion was devoted to his concerns over the attitude which he feared his family would adopt. At the termination of the interview the soldier was greatly relieved and stated that it was good to be able to discuss the worries he had been hiding. On the same day the surgeon in charge of his care continued the discussion, reassuring the soldier of faith in his character and stressing the need for the patient to regain his self esteem and face the problem. He was given the suggestion that the hand would begin to improve. The patient slept soundly that night for the first time since the pain had started and on the following morning reported that his hand hurt less. No objective changes were visible, but the soldier was encouraged to use the hand as much as possible.

On the afternoon of the day following the psychiatric interview, the patient was questioned after an intravenous injection of sodium pentothal. He told the same story as on the previous day and denied that he had sought to escape combat. While still in a hypnotic state from the barbiturate, he was given the suggestions that the pain would lessen and that the range of motion in the hand would increase from day to day.

The patient continued to sleep well with little, or no, sedation, and there was a striking alteration in his attitude and behavior. He again became friendly with other patients, kept working at the movement of his fingers and rarely complained of pain. Three days after the interview he reported that the pain was moving outward from the palm toward the periphery in progressive fashion, as had been suggested. Diminution in the flushing and sweating could be noted. A week after the interview the hand was painless, and all indications of vasomotor abnormality had disappeared; the color and sweating were similar to the condition of the left hand, and the edema and hyperesthesia had gone. The patient appeared cheerful, and he was working at occupational therapy to improve the range of motion in the ring finger. Brief daily discussions were mainly given to reassurance and encouragement.

Heat therapy was tried again after another week to learn whether it would precipitate a recurrence of the pain. The patient reported that the treatment was painless and that he believed it improved motion. Physical therapy and heat were given daily thereafter. Improvement in the range of motion of the ring finger continued steadily, and six weeks after the onset of recovery but slight limitation of extension remained and strength was excellent. The absence of the middle finger caused him no inconvenience. After several discussions concerning the situation, the soldier was returned to his unit for full duty. He had decided that, despite his reluctance to return to a unit in which he believed he was held in disgrace, it would be best for him to prove himself in combat and regain the respect of his friends.

COMMENT

The case appears to have contained all the essential components of the causalgia syndrome. The injury involved joints and peripheral nerves and resulted in the amputation of a finger. There was clear evidence of localized autonomic malfunction, as shown by the change in the color of the skin, edema, sweating and early trophic disturbance. There were acute hyperalgesia and constant burning pain, which was exacerbated by slight stimuli. The least movement was considered unbearable, and the fingers were kept motionless in a flexed position.

Recovery started immediately after the patient was helped with the handling of his emotional problems, which were resultant on the circumstances surrounding the injury. It seemed unlikely that the improvement was coincidental, as the alteration in his attitude was as pronounced as the changes in the hand. It is deemed of interest that the therapy was extremely simple. It did not involve basic personality traits or a change in actual situations or an investigation of the possibility of unconscious motivation of the accident. The situation was altered by clarifying it and by changing the soldier's attitude toward the circumstances. The catharsis of his pent-up

emotions afforded considerable relief, which was furthered by the help given him in regaining his self esteem. The suggestion given under the influence of sodium pentothal and the more casual suggestion made daily were believed to have been beneficial because the ground had been cleared by discussions of his concerns. It was fortunate that psychiatric help was offered early, before the changes had time to become fixed, and that the emotional trauma did not involve matters that were basic to his personality structure.

Although it has been clear from the literature that many persons suffering from causalgia were emotionally unstable, there has been doubt that such unilateral and localized difficulties, in contrast to more generalized autonomic disturbances, could depend on emotional influences. The present case offers striking evidence that the emotional state of the patient can, perhaps in conjunction with local stimuli arising from the traumatized area, influence the local autonomic reflexes in a single extremity.

SUMMARY

In a case of causalgia, with a typical syndrome, recovery followed promptly on simple psychotherapy.

EROTOMANIA (NYMPHOMANIA) AS AN EXPRESSION OF CORTICAL EPILEPTIFORM DISCHARGE

T. C. ERICKSON, M.D., PH.D.

MADISON, WIS.

Relatively little is known in regard to the representation of the sacral segments of the cord in the cerebral cortex of man. Penfield and Boldrey[1] (1937) recorded sensation in the opposite side of the penis following cortical stimulation but obtained no motor responses. They pointed out that the rarity of responses in the lower sacral and genital regions may be due to the comparatively small number of stimulations which the neurosurgeon is able to perform within the central fissure, or possibly to a false sense of modesty on the part of the patient. Scarff[2] (1940) observed contraction of the anal sphincter in 1 patient after electrical stimulation of the medial surface of the cerebral hemisphere.

In contrast to the paucity of observations in man, the representation of the sacral segments has been worked out with considerable precision in the cortex of the monkey (Woolsey, Marshall and Bard,[3] 1942; fig. 1). It is reasonable to suppose that the genitalia and other perineal structures in man have a similar sensory representation in the cerebral cortex of the paracentral lobule on the medial surface of the hemisphere. A priori, one would expect this area to be the occasional site of an epileptogenic lesion manifesting itself by a sensory jacksonian seizure with its onset in the genitalia. No such case had, however, come to my attention until the one presently to be discussed, nor have I been able to find a similar instance recorded in the literature.

Read at a meeting of the Chicago Neurological Society, April 11, 1944.

From the Department of Surgery, University of Wisconsin Medical School.

1. Penfield, W., and Boldrey, E.: Somatic Motor and Sensory Representation in the Cerebral Cortex of Man as Studied by Electrical Stimulation, Brain **60**: 389-443, 1937.

2. Scarff, J. E.: Primary Cortical Centers for Movements of Upper and Lower Limbs in Man, Arch. Neurol. & Psychiat. **44**:243-299 (Aug.) 1940.

3. Woolsey, C. N.; Marshall, W. H., and Bard, P.: Representation of Cutaneous Tactile Sensibility in the Cerebral Cortex of the Monkey as Indicated by Evoked Potentials, Bull. Johns Hopkins Hosp. **70**:399-441, 1942.

REPORT OF A CASE

Mrs. C. W. was first admitted to the Wisconsin General Hospital on May 18, 1939, at the age of 55, and, after study, was discharged on June 9, 1939, with a primary diagnosis of nymphomania. In the following account of her history I shall quote her own description of the sensation whenever possible.

The patient stated that she had always "enjoyed sexual intercourse," but since the age of 43 she had become increasingly "passionate." At night she would awaken with a feeling of being "hot all over," as if she were having coitus. This sensation would last about five minutes. After the first four or five weeks, it became more frequent until a year before admission (at the age of 54), when it decreased but still occurred every afternoon. Her husband suffered from hypertension and finally had a stroke in December 1938! She stated that when he could not satisfy her he made "nasty remarks and left her to herself." When the "hot feeling" was pronounced, she could obtain relief from a lukewarm tub bath, followed by packing of the vagina with cracked ice.

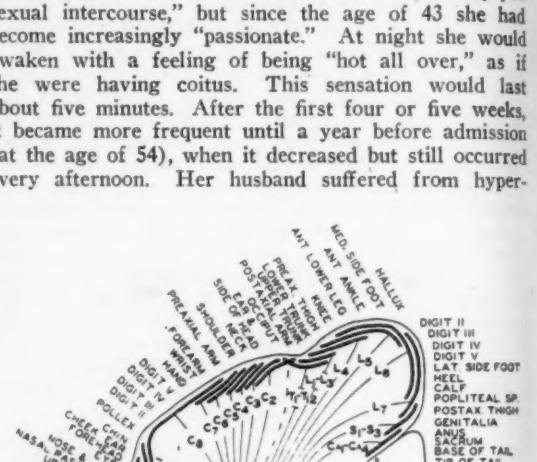


Fig. 1.—Reproduction of cortical sensory chart in the monkey (Woolsey, Marshall and Bard,[3] fig. 14). In this figure, *C*, *T*, *L*. *S* and *Ca* with their subscripts refer to specific dermatomes of projection. *F.S.* is the sylvian fissure; *F.C.*, the central fissure; *S.C.M.*, the callosomarginal sulcus; *MAX.*, the maxillary distribution; *MAN.*, the mandibular distribution, and *OPHTH.*, the ophthalmic distribution. Note the responses obtained from the perineal regions.

Ten years before this admission (i. e., about two years after the onset of the nymphomania) she suddenly felt unable to speak during one of the "hot spells"; she became "tight all over" and had "jerking movements"

of the left leg and the left side of the abdomen. At times there was a feeling of movement without actual movement. These attacks lasted for twenty minutes and recurred daily for a period of two years, but later they recurred only once every six months. At first she laughed and cried when she had the attacks, but she said she was not so hysterical later because various physicians had warned her that she would be put in a straight jacket if she did not control herself.

When the nymphomania first began, she had "an affair" with another man; but when her husband discovered it, she never again tried to satisfy herself in this fashion. When she used alcohol or perfume she thought her symptoms were accentuated. She joined the Mormon church and felt that "their strict rules saved her." Sexual relations with her husband stopped when he had the stroke. The nymphomania and her husband's impotence alienated the affection of both her husband and her children, of whom she had ten, ranging in age from 18 to 37 years.

Her menses began at the age of 13 years and occurred regularly every twenty-eight days, with an abundant flow lasting seven days. For six months before the first admission to the hospital, at the age of 55, the menstrual flow had become more scanty and irregular, and she had hot flashes. There was no chronologic relation between these menopausal symptoms and the nymphomania.

Physical examination revealed a well developed, somewhat obese, white woman. The blood pressure was 140 systolic and 90 diastolic. There were a well healed thyroidectomy scar, numerous areas of vitiligo over the chest and brown pigmentation of the eyelids. Dr. M. J. Thornton reported that pelvic examination revealed nothing abnormal except for a first degree cystocele and rectocele. Cervical smears were negative for gonococci and yeast, but Trichomonas was present. Biopsy of the endometrium showed a normal follicular reaction. Roentgenograms of the chest and sinuses revealed nothing abnormal. Hypertrophic arthritis of the cervical portion of the spine was observed. Roentgenographic study of the left shoulder showed nothing abnormal. No other pertinent observations were recorded at this time. In view of the fact that the nymphomania was her major symptom, roentgen ray therapy (four treatments of 200 r each) was given to stop ovarian function. The patient was discharged on June 9, with a diagnosis of nymphomania and first degree rectocele and cystocele.

The patient was readmitted to the hospital on Feb. 23, 1940. Her daughter stated that since discharge there had been no sexual irregularities as far as was known but that she still had an abnormal desire for intercourse. In September 1939 she had a severe and profuse menstrual period. The same month she had convulsive seizures, which always began in the left leg after an aura consisting of a "passionate feeling." During these attacks, she bit her tongue; her eyes rolled back in her head, and her body stiffened out. The first major seizure was followed by a partial paralysis of the left side of the body. Phenobarbital, ½ grain (0.032 Gm.), had been efficacious in cutting down the number of seizures. The patient's daughter stated that her mother had been nervous and at times irrational and unreasonable. She had threatened to take her own life on several occasions. The patient had no further major seizures from September 1939 to February 1940; however, she had several slight attacks, during which she shook all over for several minutes. She had menstrual periods in December 1939 and February 1940.

In addition to the lesions previously recorded, physical examination revealed a large, soft, movable mass, probably a lipoma, over the right clavicle; prominent inguinal adenopathy; apical and basal systolic murmurs, and a blood pressure of 126 systolic and 70 diastolic. Neurologic examination disclosed paresis of the entire left upper extremity and, to a lesser degree, of the lower extremity. The face was not involved. Reflexes were exaggerated on the left side, but a Babinski sign could not be elicited. There was no involvement of the tongue or face. The fundi were normal, showing relatively little sclerosis. The results of pelvic examination were essentially normal.

Routine laboratory studies revealed normal urinary constituents, a hemoglobin concentration of 13.4 Gm. per hundred cubic centimeters and a white blood cell count of 7,250, with a normal differential count. The sugar content of the blood was 86 mg. and the nonprotein nitrogen 31 mg. per hundred cubic centimeters; the Wassermann reaction of the blood was negative. A lumbar puncture revealed an initial pressure of 236 mm. of water. The Wassermann reaction of the cerebrospinal fluid was negative; the colloidal gold curve was 1222100000; the reaction for globulin was faintly positive, and the cell count was zero.

The report of the roentgenographic examination of the skull (Dr. Lester Paul) was as follows: "The sella is normal in size, but the posterior portion of the floor and the posterior clinoid processes appear decalcified and thinned. The anterior clinoid processes are intact. The cranial bones elsewhere are of normal appearance. There is no abnormal intracranial calcification or other localizing evidence of intracranial neoplasm. The changes noted in the sella, however, are suggestive of erosion from extrinsic pressure." A roentgenogram of the chest showed no significant change from the film taken the previous summer. A roentgenogram of the dorsal portion of the spine revealed slight scoliosis to the left side and slight hypertrophic change throughout that portion of the spine. There was an old fracture in the posterior arc of the left eleventh rib, with evidence of callus.

It was the opinion of the medical and psychiatric staff at this time that the signs presented by the patient were the residuals of a vascular lesion in the right motor cortex, but that the presence of a neoplasm had not been entirely ruled out. In view of the patient's continuing menses, it was felt advisable to provide several more roentgen ray treatments to the ovaries; and, after consultation with the department of roentgenology, she was given four additional treatments, consisting of 200 r each. In addition, she received physical therapy to the left shoulder and noted some improvement under that regimen. Thiamine hydrochloride, 50 mg. daily, was provided, as well as theophylline ethylenediamine, 1½ grains (0.097 Gm.) four times a day. The final diagnoses at the time of discharge, on April 22, 1940, were cerebral vascular accident with symptomatic grand mal epilepsy, nymphomania, vitiligo, lipoma and menopausal syndrome.

Because of a gradual increase in the left hemiplegia, the patient was readmitted to the hospital on June 18, 1943. During the two year interval since the previous admission she had spent most of her time in a nursing home. The symptoms of nymphomania had persisted. There had been a slight show of blood on two or three occasions during the year. The patient said that the roentgen ray therapy to her ovaries had not helped her menses, and she wished that she had left her husband and married another man "who could take care of her" (intercourse). At this time she described the "passionate feeling" as being accompanied by staring of the eyes so that she could not move them, and then by feeling that the yolk of an egg was running down

her throat (apparently a postnasal discharge). She also noted that when she blew her nose the left big toe drew upward.

Examination by Dr. Mabel Masten on June 21 revealed that there had been a gradual increase in the left hemiparesis which originally followed epileptic seizures, in 1939. The left side of the face was weak, and the left arm and leg had become spastic, with contracture of the left shoulder joint. A grasp reflex and a Wartenberg sign were elicited on the left side. There was wrist and ankle clonus. Dr. Masten expressed the belief that the findings strongly suggested a cerebral tumor, such as a slowly growing meningioma.

Lumbar puncture, with the patient recumbent, revealed an initial pressure of 250 mm. of water. The spinal fluid contained no cells, and the protein content was 35 mg. per hundred cubic centimeters; the colloidal gold curve was normal, and the Wassermann reaction was negative. Ophthalmoscopic examination showed normal fundi. Roentgenographic examination of the skull showed no change since the previous examination, when there were thinning and decalcification of the dorsum sellae. In the occipital region an area of translucency 1 cm. in diameter was thought to represent a congenital ossification defect, since it was midline in position and had not changed over a period of years. The patient had a jacksonian seizure on the left side on the day prior to operation; this was similar to the seizures previously described.

Pneumoencephalographic study, carried out on July 1, 1943, revealed a shift of the midline structures from right to left, with flattening of the roof of the right lateral ventricle to a level at least 1 cm. lower than that of the left lateral ventricle (fig. 2). There was absence of air in the subarachnoid channels over the right hemisphere except for filling of the island of Reil, which was lower in position than the corresponding structure on the left side. It was concluded that there was an expanding, space-occupying lesion in the right parietal parasagittal region.

An osteoplastic craniotomy was performed in the right parietal region, with the use of local anesthesia, on July 1, 1943. The tumor was noted at the upper end of the rolandic sulcus between the medial surface of the hemisphere and the falx (fig. 3). The tumor was completely removed, and its area of attachment to the falx was coagulated with the Bovie unit.

On microscopic examination (fig. 4) this tumor was observed to be composed of numerous endothelial cells and small vascular channels, some of which were occluded by a hyaline material. There was no variation in cell size and no mitotic figures. A diagnosis of hemangioma was made by Dr. W. H. Jaeschke.

Stimulation of the cortex with the thyratron stimulator gave slight responses in the arm and face area but none in the leg area. The patient was not sufficiently cooperative for elicitation of any sensory responses. The postoperative course was without any unusual incident except for the occurrence of a single local clonic seizure involving the left arm alone on the fifth postoperative day. The patient occasionally complained of pain in the left arm and leg, which was felt to be due to contractures following the long-standing hemiplegia. The pain improved with physical therapy. The subjective symptoms of nymphomania were present on only one occasion after operation, from which her convalescence was rapid and otherwise uncomplicated.

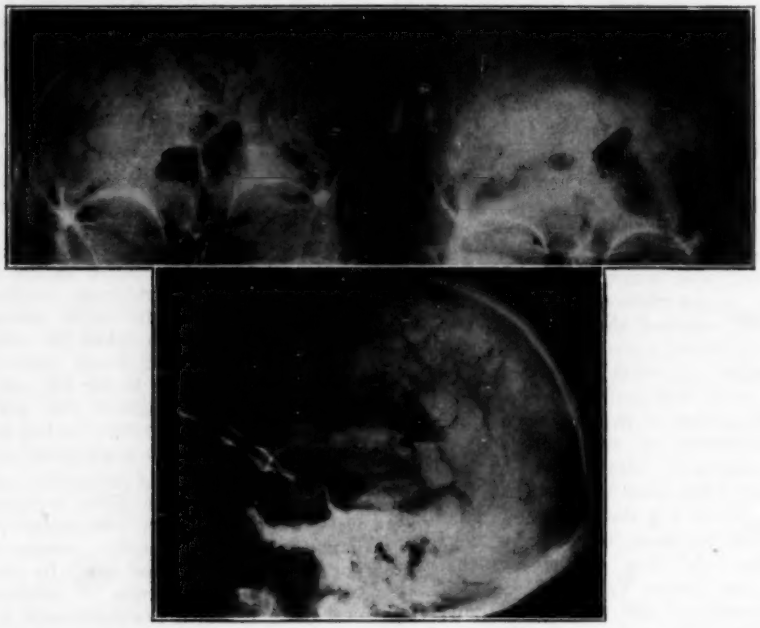


Fig. 2.—Pneumoencephalograms of the patient, showing the location of the parasagittal tumor.

A Rorschach test, done on the thirtieth postoperative day by Dr. M. Harrower-Erickson, was reported as follows: "The record is within normal limits. There is no indication whatever of the typical organic personality pattern. Another surprising feature is the speed with which the responses are made and the number of original responses that are given. There are no unusual sexual responses. Evidence of good contact with the environment and adequate control is present. While the record is not one of a particularly intelligent person, there is no suggestion of intellectual deterioration."

Partial left hemiplegia persisted when the patient left the hospital after operation. She wrote frequent letters revealing that she was resentful of the use of roentgen ray therapy to the ovaries, and she also expressed fear because of persistent paralysis that she might have another cerebral tumor. In July 1944, a year after removal of the tumor, she returned to the hos-

pital for examination. She had had no headaches and no convulsive seizures. Once, while helping to lift another patient, she had noted shaking of the left arm, which was interpreted as clonus. When asked if she had had any "passionate spells" since operation, she said, "No, I haven't had any; they were terrible things." Closer questioning revealed that she had what she interpreted as normal sexual desire, but she insisted that this did not have the insistent character and uncontrollability of the previous attacks. The strength in her leg had improved so that she was able to walk well, but the hand had shown little improvement.

She had had no urinary difficulty; her appetite was good, and she had had no vertigo, tinnitus or syncope.

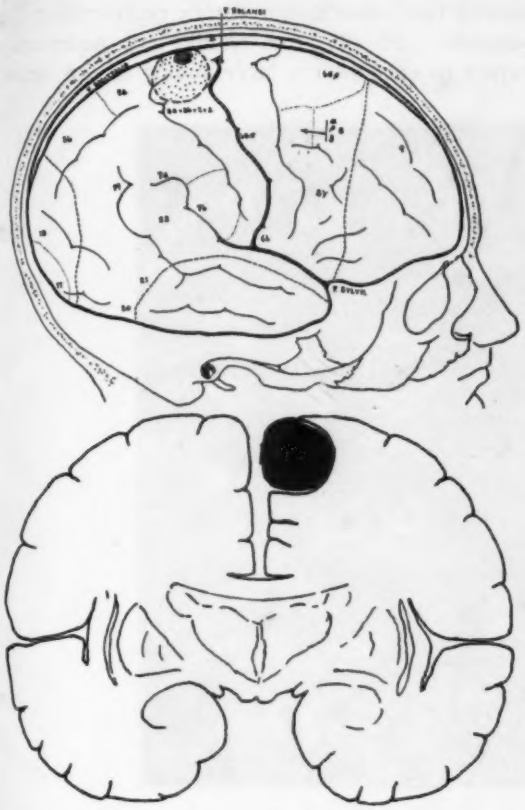


Fig. 3.—Diagrams illustrating the location of the neoplasm as disclosed at operation.

She had not had any menstrual bleeding except for a slight show on two days in the autumn of 1943.

Examination at this time showed that the patient still had spastic left hemiplegia, which was complete in the arm and partial in the leg. There were astereognosis in the left hand and loss of skin writing and position sense. The wound was well healed, and the cranial nerves were normal.

COMMENT

In this case nymphomania was clearly the result of a tumor which caused excitation of the topical projection of the genital structures on the medial surface of the cerebral hemisphere. For two years the patient presented no symptoms other than the nymphomania. The significance of this symptom was only evident when the same sensory experience was followed by jacksonian seizures and, finally, by progressive hemiplegia.

The sensory representation of the genitalia has been demonstrated in monkeys to lie in the paracentral lobule at the upper lip of the callosomarginal sulcus (fig. 1; Woolsey, Marshall and Bard [3]). In my patient electrical stimulation of the cortex gave a few responses in the arm area of the precentral gyrus but was not satisfactory in the immediate vicinity of the lesion because of the depression of function, caused no doubt by removal of the vascular tumor. The tumor was attached to the falx and impinged on the paracentral lobule on the medial surface of the hemisphere just above the sulcus cinguli, an area homologous to that which contains the sensory representation of the genitalia in monkeys.

The patient's description of her initial sensation did not enable me to localize it to any particular portion of the genitalia, nor was it described as a numbness or tingling similar to the usual sensory seizures. It seemed to be mainly contralateral to the cortical lesion. To quote the patient: "These spells are just the same as ordinary intercourse, but only on the left side. They are relieved for a while after intercourse, but I could have intercourse all the time without very much relief." She denied any attempt at masturbation or recent homosexual activity. The patient did not distinguish this sensation from the normal, and it led her to seek sexual intercourse. Although this "passionate feeling," as she called it, had the usual agreeable qualities of the normal, its frequency and uncontrollability, and the fact that it was later followed by a jacksonian epileptic march, made it annoying and distasteful to her.

Thorough and repeated gynecologic examinations failed to reveal any peripheral cause of the nymphomania. My colleagues in gynecology tell me that local changes in the pelvis are rarely responsible for this symptom and that a patient with this disturbance is usually referred to the psychiatrist.

According to Forel [4] (1926), erotomania (nymphomania) is especially noted with acute mania and with the early stages of dementia paralytica and senile dementia, as well as temporarily or permanently with other psychoses. It is worthy of note that my patient showed no psychotic traits either in the Rorschach test or on clinical examination. Her malady might well have been

4. Forel, A.: The Sexual Question: A Scientific, Psychological, Hygienic and Sociological Study, ed. 2, translated by C. F. Marshall, New York, Physicians and Surgeons Book Company, 1926.

expected to give rise to indirect psychologic changes, as it did.

Many of the recent papers on nymphomania discuss the effect of endocrine preparations, but there is no consensus in regard to the results with the various glandular substances. In the present case artificial menopause induced by irradiation of the ovaries, only partially effective, it is true, had no influence on the nymphomania; in fact, the condition progressed steadily and ceased only after the removal of the cerebral tumor. That the nymphomania was more severe in association with the menstrual periods was no doubt due to changes in the neoplasm as the result of premenstrual edema. The accentuation of symptoms due to cerebral tumor in this way is well known. The late onset of the menopause suggests the possibility that the delay was caused by the abnormal or excessive innervation of the genitalia.

Although the lesion was no doubt close to the cortical representation of the urinary bladder, the patient at no time had any urinary difficulty, owing perhaps to bilateral innervation of this structure. This particular tumor no doubt varied greatly in size because of its vascular nature. In fact, the pneumoencephalogram suggested the presence of a much larger tumor than was actually removed at operation, and one can assume that this was due to a variation in its size from time to time.

Whether the type of lesion presented by this patient represents an extreme rarity among patients with symptoms of nymphomania or whether there are other, similar, cases which have gone unrecognized is impossible to ascertain until psychiatrists and neurologists direct their attention to the possibility of the existence of an organic lesion in the sensory area of the cortex in patients with erotomania (nymphomania or satyriasis). Either a tumor or an atrophic lesion might be expected to produce such a symptom if it caused irritation of the area of the sensorimotor cortex representing the genitalia. Finally, one should not necessarily expect to encounter a large tumor as the cause, for even a small cicatrix or vascular lesion might theoreticaly give rise to an epileptiform discharge in this region.

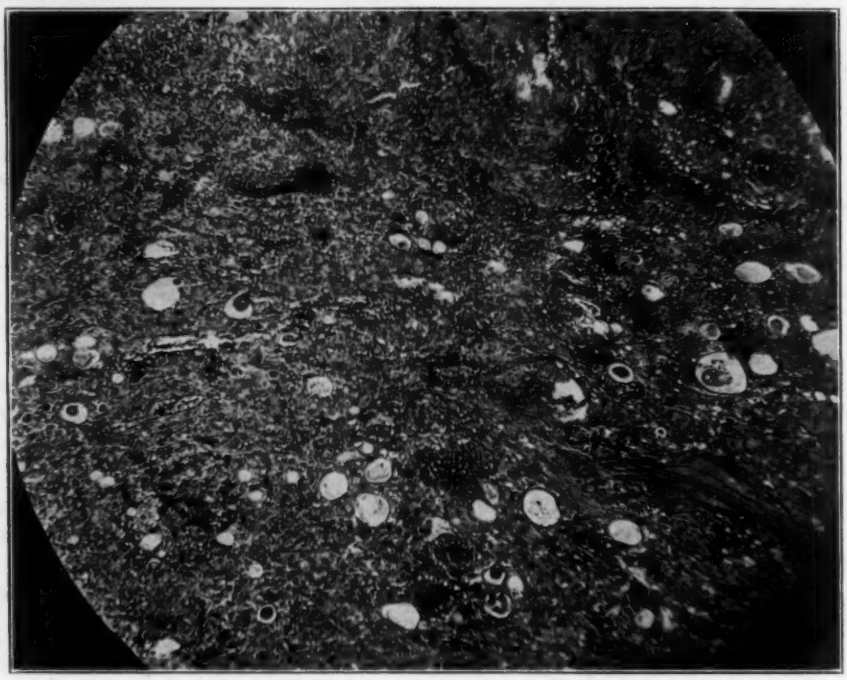


Fig. 4.—Photomicrograph of encapsulated hemangioma removed at operation.

SUMMARY

Erotomania as the initial manifestation of a cortical epileptiform discharge has not previously been described. In the present case the patient began to manifest nymphomania, which occurred in paroxysms of short duration, at the age of 43 years. Two years later these spells of nymphomania served to usher in typical jacksonian seizures, spreading first to the left lower extremity. With repetition of the focal seizures postictal paralysis supervened. Examination revealed the presence of a neoplasm, causing excita-

tion of the topical projection of the genital structures in the right paracentral lobule. A year after operative removal of the neoplasm the patient no longer exhibited nymphomania.

DISCUSSION

DR. VICTOR E. GONDA, Chicago: The lesion being so near the paracentral lobule, I should like to ask whether this patient ever had any subjective or objective urinary difficulties.

DR. RALPH C. HAMILL, Chicago: I had a patient, a girl aged 19, with a tumor of the pineal gland the size of a small olive. She had definite nymphomania. I wonder whether the pineal gland or the paracentral lobule was irritated by the tumor.

DR. THEODORE C. ERICKSON, Madison, Wis. My patient did not have any urinary complaints. I do not see how a pineal tumor could come into contact with this region of the cortex. My associates and I have seen several patients with lesions of the frontal lobe who exhibited increased libido, and I always assumed it was due to lack of inhibition.

NOTE:—In the discussion following presentation of this case before the Montreal Neurological Society Feb. 7, 1945, Dr. Wilder Penfield described a patient with a lesion of the temporal lobe who exhibited sexual ideas as a component of his dreamy states. In the cases reported by Dr. Hamill and Dr. Penfield there was no doubt discharge from a higher level of representation, in the jacksonian sense, than that in the present case.

State of Wisconsin General Hospital.

Case Reports

ELECTROENCEPHALOGRAPHIC CHANGES IN A CASE OF SUBARACHNOID HEMORRHAGE

N. Savitsky, M.D.; B. L. Pacella, M.D., and F. D. Stern, M.D., New York

Despite an extensive literature dealing with subarachnoid hemorrhage, we have been unable to find any electroencephalographic studies of this disease. The occurrence of spontaneous bleeding into the subarachnoid space of a patient already in the hospital who had been under observation for a period and had had a previous electroencephalogram afforded an unusual opportunity to follow the electrophysiologic changes which occurred. The electroencephalographic data furnish cogent evidence that significant changes occur within the brain. These data corroborate the clinical and pathologic evidence that such changes do occur within the brain in cases of subarachnoid hemorrhage, even when the source of bleeding is not intracerebral.

REPORT OF CASE

History.—M. H., a man aged 50, was admitted to the Montefiore Hospital on March 4, 1943, with complaints of difficulty in walking, pain in the left arm and a feeling as though "the arm were broken and the cracks were trying to get together." For several years prior to admission he had had moderately severe occipital headaches, which were frequently relieved by acetylsalicylic acid. For two or three years projectile vomiting, usually not preceded by nausea, had at times accompanied these headaches. He had also complained of ready fatigue since the onset of his illness. He had had sharp pains in the arms and, less frequently, in the legs for six years. A few attacks of diplopia had occurred over a period of about five years. There was an unclear history of iritis about two years before admission.

On July 4, 1942 the patient attended a picnic with his wife, where he ate frankfurters. On the way home he felt ill and vomited. The next morning he had chills and complained of dizziness, with objects in the room apparently turning around. His wife noticed that his face was "pulled to the right." This "pulling of the face" gradually became worse over a period of one week. About October 1942 he began to show improvement.

At about this time the patient also noticed weakness of the left side of the body. On July 13 he was admitted to a hospital, where he received physical therapy and intravenous injections of typhoid vaccine, with improvement. During the few months before his admission to the Montefiore Hospital he became worse, and walking became increasingly difficult, until he required support to get about. His wife added that his speech had become less clear. She also described personality changes; he became more abrupt and less courteous.

The past and the family histories were without significance.

From the Electroencephalographic Laboratory, Montefiore Hospital for Chronic Diseases, Dr. S. P. Goodhart, Director, and the New York State Psychiatric Institute and Hospital, Dr. Nolan D. C. Lewis, Director.

Examination.—Physical examination showed no evidence of disease of the internal organs. The blood pressure was 140 systolic and 90 diastolic. The fundi showed arteriosclerotic retinopathy.

Neurologic study revealed shuffling gait, with a tendency to marche à petits pas; weakness of the entire left side of the body; increased deep reflexes, especially of the left side, and a Babinski sign bilaterally, which was more definite on the left side.

Roentgenographic examination of the chest showed slight enlargement of the heart, with a rounded left ventricle and moderate tortuosity and dilatation of the aorta. A roentgenogram of the skull revealed nothing abnormal.

Laboratory Data.—Urine: The reactions for albumin and sugar were negative.

Blood: Determination of the chemical constituents of the blood showed 14.3 mg. of urea nitrogen and 95 mg. of sugar per hundred cubic centimeters of blood. The hemoglobin concentration was 91.8 per cent. The red cells numbered 5,110,000, and the white cells 9.150, with a differential count of 42 per cent polymorphonuclear leukocytes, 48 per cent lymphocytes, 4 per cent eosinophils and 6 per cent mononuclears.

The Wassermann and Kahn reactions were negative.

Spinal Fluid: The fluid was slightly cloudy. The Pandy reaction was 1 plus. The cell count showed 739 crenated cells, 5 fresh red cells and 2 white cells (probably the result of trauma) per cubic millimeter.

The initial pressure was 190 mm. of water; the final pressure, after removal of 10 cc. of fluid, was 120 mm. There was no sign of blood.

The sugar content was 76 mg. and the protein content 16 mg. per hundred cubic centimeters.

Course of Illness.—The patient's condition was relatively stationary until Feb. 3, 1944. On that day he complained of inordinate weakness. During the evening of the same day he began to have projectile vomiting, vertigo, intermittent sensations of coldness and generalized tremulousness. Examination the same day revealed a blood pressure of 220 systolic and 160 diastolic; his pulse was rapid. Except for a bilateral Hoffmann sign, the neurologic signs were unchanged.

During the next few days the patient continued to vomit; he became drowsy and slept a great deal. Rigidity of the neck appeared. The temperature rose slowly, reaching 103.8 F. on February 8, and then receded slowly, becoming normal again on February 15. He improved slowly. Some drowsiness persisted.

On February 8 lumbar puncture yielded a pinkish yellow fluid. The initial pressure was 340 mm of water, and the final pressure, after removal of 10 cc., was 220 mm. The cell count revealed 11,000 red blood cells, with a few crenated forms, and 160 white cells; the total protein content was 69 mg. per hundred cubic centimeters.

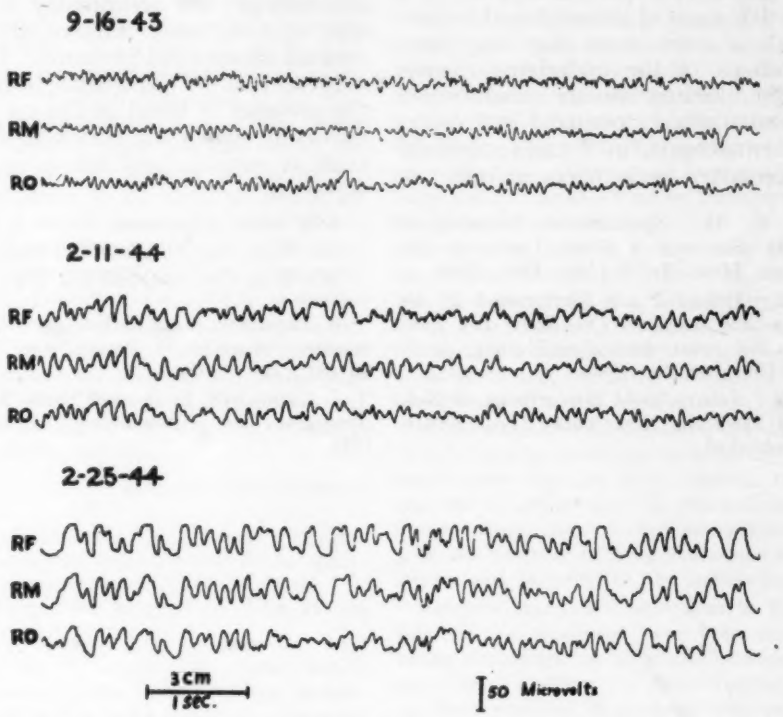
On February 10 spinal tap revealed xanthochromic fluid. The Pandy reaction was positive. A cell count showed 273 red blood cells, mostly crenated, 333 polymorphonuclears and 69 lymphocytes. The total protein content was 64 mg per hundred cubic centimeters.

Another spinal tap, on March 16, revealed a clear fluid, a negative Pandy reaction, an initial pressure of 130 mm., and a final pressure, after removal of 10 cc., of 80 mm. per hundred cubic centimeters. The protein content was 52 mg. per hundred cubic centimeters.

Electroencephalographic Observations. — Electroencephalographic tracings were obtained on three separate occasions. The first record was taken Sept. 16, 1943, several months prior to the subarachnoid hemorrhage. This record showed much 7 to 8 cycles per second rhythm over the entire cortex, in addition to random 5 to 6 cycles per second activity. The pattern suggested widespread cerebral disturbance and was consistent with the presence of chronic generalized cerebral changes. No focal abnormalities were evident (figure).

On Feb. 11, 1944, approximately one week after the subarachnoid hemorrhage, an electroencephalogram showed considerably more abnormal activity than was previously recorded, with higher amplitude and a greater incidence of 5 cycles per second serial activity, appearing over the entire brain (figure).

On February 25 another electroencephalogram showed progression in the degree of abnormality, with numerous 2 to 4 per second waves of high amplitude appearing over all regions of the cortex. The last record indicated an increase in intensity of the physiologic disturbance in the brain since the previous electroencephalogram (figure).



Electroencephalograms taken before (Sept. 16, 1943) and after (Feb. 11 and 25, 1944) subarachnoid hemorrhage.

COMMENT

We have found no reports on electroencephalographic studies in cases of subarachnoid hemorrhage in which tracings were made before and after the incident. Although the first record taken prior to the hemorrhage revealed widespread cerebral disturbance, possibly related to chronic degenerative (vascular [?]) changes in the brain, subsequent records revealed a definite increase in this disturbance. The important point in these studies is the observation that the abnormality in the electroencephalogram continued to increase for some time after the hemorrhage in spite of the fact that there were no evidences of increased intracranial pressure or repeated bleeding in the subarachnoid space. This suggests that the observed electrocortical abnormalities are not related solely to the mechanical effect or pressure of the blood on the cortex, but probably are due to other factors in which the cortex is directly affected.

The hypothesis that intracortical changes occur in cases of subarachnoid hemorrhage is in conformity with the previously expressed opinions of several investigators. Bagley,[1] after injecting blood into the subarachnoid and cisternal spaces of dogs, demonstrated the existence of small areas of cortical damage in which the blood had penetrated into the depths of the sulci. Strauss and associates,[2] in his autopsy material, showed that subarachnoid hemorrhage is often accompanied by injury to the cerebral cortex.

1. Bagley, C.: Blood in the Cerebrospinal Fluid: Resultant Functional and Organic Alterations in the Central Nervous System, Arch. Neurol. & Psychiat. **17**:18 (July) 1938.

2. Strauss, I.; Globus, J. H., and Ginsburg, S. W.: Spontaneous Subarachnoid Hemorrhage, Arch. Neurol. & Psychiat. **27**:1080 (May) 1932.

Friedman [3] reported 4 cases in which, in addition to signs of subarachnoid bleeding, evidence of focal lesions of the brain was presented. He stated that the hemiplegia in these cases occurred as a result of seepage of blood into the brain. Noetzel [4] demonstrated that when small amounts of trypan blue are injected into the subarachnoid space, the brain substance becomes colored. He reported 2 cases of old subarachnoid hemorrhage in which there was evidence of diffusion of blood into the brain substance. He noted hemosiderin in the cerebral cortex, the cerebellum and the periphery of the spinal cord. Such continued seepage of blood into and disintegration within the brain may account for the increase in the abnormality of the electroencephalogram.

One of us (N. S.) [5] reported sequelae in 8 per cent of his 100 cases of subarachnoid hemorrhage, although in some cases they may have been manifestations of the underlying disease which caused the bleeding into the subarachnoid spaces. Jacksonian attacks occurred in 2 cases; homonymous hemianopsia, in 2 cases; aphasia, in 2 cases; secondary optic nerve atrophy, in 1 case, and a severe memory defect, for a whole year, in 1 case. Mental sequelae in the form of memory defect and Korsakoff psychosis have been described.[6] These mental changes often become severe a few days after the onset, sometimes lasting a few weeks. Carmichael and Stern [7] suggested that the hemolyzed blood acts as a toxic agent, pointing to the latent interval of several weeks between the onset of the subarachnoid hemorrhage and that of the mental syndrome.

SUMMARY

In a case of subarachnoid hemorrhage in which electroencephalographic tracings were made before and, on two separate occasions, subsequent to the hemorrhage, the electroencephalogram revealed diffuse changes after the hemorrhage; the abnormality increased after a time of observation without any associated increased intracranial pressure. This observation suggests that the disturbance is due not merely to the presence of blood on the cortex but to other factors in which the cortex is directly affected, such as seepage into the brain and its disintegration.

1882 Grand Concourse.

722 West One Hundred and Sixty-Eighth Street.

671 West One Hundred and Sixty-Second Street.

3. Friedman, E. D.: Spontaneous Subarachnoid Hemorrhage with Signs of a Focal Lesion in the Brain, J. Mt. Sinai Hosp. **5**:255 (Nov.-Dec.) 1938.

4. Noetzel, H.: Diffusion von Blutfarbstoff in der inneren Randzone und äusseren Oberfläche des Zentralnervensystems bei subarachnoidaler Blutung, Arch. f. Psychiat. **111**:129 (Jan. 10) 1940.

5. Savitsky, N.: Subarachnoid Hemorrhage, in Nelson's Loose Leaf Medicine, New York, Thos. Nelson & Sons, to be published.

6. Tarachow, S.: The Korsakoff Psychosis in Spontaneous Subarachnoid Hemorrhage, Am. J. Psychiat. **95**:887 (Jan.) 1939.

7. Carmichael, E. A., and Stern, R. O.: Korsakoff's Syndrome: Its Histopathology, Brain **54**:189 (June) 1931.

Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Physiology and Biochemistry

FUNCTIONAL ORGANIZATION OF THE MEDIAL ASPECT OF THE PRIMATE CORTEX. PERCIVAL BAILEY, GERHARDT VON BONIN, EDWARD W. DAVIS, HUGH H. GAROL, WARREN S. MCCULLOCH, EPHRAIM ROSEMAN and ANIBAL SILVEIRA, J. Neurophysiol. **7**:51 (Jan.) 1944.

Bailey and his collaborators used the strychnine technic to determine the physiologically distinguishable areas on the medial surface of the cerebral cortex in Macaca mulatta and chimpanzees. The authors found area 24, in the anterior portion of the gyrus cinguli, to be a suppressor area. From area 23, in the posterior and superior part, impulses could be traced to the preoccipital and parastriate areas and, in the macaque, to the anterior nucleus of the thalamus. Area 29, in the gyrus cinguli and near the splenium of the corpus callosum, had no other cortical connections but in the macaque projected to the anterior nucleus of the thalamus. Along the sulcus cinguli a region homologous with areas 32 and 31 was found to receive connections from all known suppressor areas of the cortex but did not of itself project to these areas. Commissural connections were demonstrated for area 32, but not for area 31. The firing characteristics were determined in the chimpanzee for areas on the medial surface of the frontal lobe. These areas may correspond with Brodmann's areas 10, 11 and 12. In the macaque these areas could not be identified.

FORSTER, Philadelphia.

STUDIES ON THE TREATMENT OF EPIDEMIC EXPERIMENTAL POLIOMYELITIS WITH POLIOMYELITIS ANTISTREPTOCOCCIC SERUM: SUMMARY OF RESULTS. E. C. ROSENOW, Proc. Staff Meet., Mayo Clin. **18**:403 (Oct. 20) 1943.

Rosenow summarizes the results of his studies, which, he believes, indicate a causal relation of the streptococcus to poliomyelitis, the proof being the production of the classic clinical and pathologic picture of poliomyelitis in monkeys with virus derived from streptococci.

In 1916 Rosenow first immunized horses with freshly isolated strains of the living streptococcus of poliomyelitis which he claims to have obtained from human beings. Later he employed strains freshly isolated from the spinal cords of monkeys which had died of experimental poliomyelitis after inoculation of the virus. At the end of the period of immunization the antistreptococcic horse serum, in extremely high dilutions, agglutinated specifically the poliomyelitis type of streptococcus. It protected rabbits against inoculations with the streptococcus and monkeys against inoculation with poliomyelitis virus.

Immune serum was first employed for patients during the 1917 epidemic. The serum was administered as soon as the diagnosis was established. The mortality rate in an untreated group of 23 patients was 35 per cent. Of the 58 patients who received the serum, 10 (17.2 per cent) died. Aside from the 7 patients who were practically moribund at the time of the first serum treatment and died, 3 (5.9 per cent) of 51 patients died for whom the serum might have been beneficial. Paralysis did not develop in any of the 19 patients to whom serum treatment was given before its onset, and all promptly recovered. Patients who showed evidence of bulbar involvement, and even those in the early stages of partial or complete coma, often responded favorably to administration of the serum, provided it was given soon after the onset of these symptoms.

The current method of preparation of the antiserum is as follows: Freshly isolated dense suspensions of streptococci are placed in glycerin (2 parts) and a 25 per cent solution of sodium chloride (1 part) and kept in a refrigerator. Antigenic specificity is preserved almost indefinitely. All subsequent batches of antistreptococcic serum used for treatment are prepared by diluting such dense suspensions as are needed for injections throughout the period of immunization.

Of the total of 2,664 patients who were treated with the serum, 252 (9.6 per cent) died, as compared with 583 (21.3 per cent) of 2,737 patients in the same epidemic who were not given serum. In experiments with monkeys, the animals who were given serum exhibited a mortality rate one-half to one-third that of the untreated control group.

In the course of these studies, the euglobulin fraction of poliomyelitis antistreptococcic serum was found diagnostic when employed in a cutaneous test. Ninety-two per cent of 324 persons ill with poliomyelitis for from one to fifteen days showed an erythematous patch of 5 sq. cm. or more in from five to ten minutes after the intradermal injection of the euglobulin fraction.

Rosenow states that objections to the general adoption of this treatment have been removed since his recent demonstration of microdiplococci in filtrates of the virus. Further, the classic picture of the disease has been produced in monkeys with virus derived from the streptococcus, and the diagnostic and preventive action of the serum has been demonstrated.

GUTTMAN, New York.

ON THE MODE OF REPRESENTATION OF MOVEMENTS IN THE MOTOR CORTEX, WITH SPECIAL REFERENCE TO "CONVULSIONS BEGINNING UNILATERALLY" (JACKSON). F. M. R. WALSHE, Brain **66**:104, 1943.

Walshe points out that the first indication of a representation of movement and of function in the cerebral cortex was deduced from clinical observation. The clinical neurologist today, viewing the knowledge at hand regarding the nature of the cortical representation of movements, finds two apparently unrelated sources of information: (1) the literature of electrical stimulation of the cortex, presenting the picture of a mosaic of excitable points, each yielding a characteristic motor response, as well as the instability of the

excitable cortex, as evidenced by facilitation, deviation and reversal; and (2) the clinical phenomena of jacksonian fits, with their three predominant foci in the motor cortex, resulting in movements of the thumb and index finger, the angle of the mouth and the hallux. The literature on experimental physiology of the motor cortex has been primarily oriented along anatomic lines; that is, it has been more concerned with the "where" than the "how" of the cortical representation of movement. Jackson pointed out that the cerebral cortex represents sensorimotor processes, and not the performing parts. That muscles themselves are not represented in the cortex is indicated by the common clinical experience of paralysis of the extensors of the wrist in voluntary extension, with the presence of powerful synergistic contraction in forced grasping. Through study of the movements elicited by electrical excitation or disease processes of the cortex, the nervous mechanisms involved in a given movement have been determined, and so the movement has come to be considered localized, or represented. Building up on this basis produced general principles of cortical representation and of the mode in which the cortex initiates movement. Thus used, "representation" means all those processes in the cortex by which these visible results are brought about. However, according to Jackson's hypothesis, the motor cortex represents all the movements which an individual organism is capable of initiating. Thus, a pattern of excitation must exist for each purposive movement, and the leading motile parts must have the most extensive representation; the greater the spatial extension of representing cortical structures, the more complete must be the integration. The motor cortex must be considered not as a mosaic of abrupt localizations but as a complex pattern of overlapping and graded representations. Therefore, after a focal lesion, while the functions of the destroyed area are not taken over by other areas, the vast repertory of movement left may allow the functional deficit to be hidden; on the contrary, a stimulating lesion may release a widespread convulsion without necessarily a wide distribution of the excitatory process through the cortex. Walshe points out the difficulty in reconciling the theories of punctate localization with the phenomena of facilitation, deviation and reversal of response, but on the basis of Jackson's hypothesis of cortical representation, these phenomena are accounted for by the changes in the relative thresholds of excitability in the different patterns of excitation. Each focus in the motor cortex has through neuronal connections the substratum of many patterns of excitation, but one of these is primary. Appropriate antecedent local stimulation will bring about facilitation by lowering the threshold of excitability, so that the change is not spatial, but is due to deviation of response. Therefore deviation, as well as augmentation and reversal, of response, is a consequence of facilitation. Coordination in time, resulting in the orderly sequence of movement, probably has as its primary factor facilitation. A destroying lesion of the cortex, in both man and experimental animals, is followed by partial return of function. This, Walshe contends, is inexplicable on the basis of the theory of punctate localization but is consistent with Jackson's hypothesis; in other words, moving parts must have wide representation in the cortex, and cortical points must contain many representations. Walshe reviews the clinical features involved in convulsions beginning unilaterally and indicates those which tend to corroborate Jackson's hypothesis of representation and the foregoing correlation of that hypothesis with present neurophysiologic observations. Since a convulsion may spread although cortical discharge may remain restricted, and since the patterns of unilateral seizures beginning in two different peripheral parts differ, Walshe concludes that the field of convulsion in the musculature is probably always wider than the field of cortical excitation. The compound order of spread of a unilateral seizure (increase in intensity as well as in distribution) is explicable on Jackson's hypothesis, but not on the theory of punctate localization. The onset of jacksonian seizures in one of three areas is not explicable on the basis of the punctate theory but can be accounted for only by Jackson's hypothesis, and these three "leading parts" probably have the widest fields of low threshold excitability. The spread of unilateral seizures is not always consistent with the topographic charts of the motor cortex; these exceptions are consistent with the jacksonian concept of representation. Jackson maintained that movements of both halves of the body were represented in the motor cortex of each hemisphere, and so focal convulsions from one motor cortex could become generalized. Walshe compares this with the frequent observation of bilateral neurologic signs in cases of severe hemiplegia. Focal seizures characterized by sudden transient motor impairment or loss of speech may afford confirmation of the presence of inhibitory areas of the cortex. The same mechanism may explain the postseizure flaccid coma.

FORSTER, Philadelphia.

Psychiatry and Psychopathology

A NEUROPSYCHIATRIC VIEW OF GERMAN CULTURE. RICHARD M. BRICKNER and L. VOSBURGH LYONS, J. Nerv. & Ment. Dis. **98**:281 (Sept.) 1943.

Brickner and Lyons point out that the technics of neurology, psychiatry, psychology and anthropology have had little acceptance thus far in the solution of group problems, the oversimplifications of economics and politics still holding sway. Knowledge of group behaviors gained through use of these sciences are applied to the problem of the German cultural pattern.

There has existed for more than one hundred years a dominant German cultural attitude, characterized by systematized megalomania, sense of mission, suspiciousness, sense of persecution, retrospective falsification, projection, mysticism, lack of critical judgment, lack of humor, extreme use of rationalization and impeccably logical elaboration of original premises. This constellation of paranoid thinking is a dominant trait in German culture and is considered to be not only acceptable but desirable. It is dangerous to the rest of the world because it is contagious, murderous and enslaving and attempts to be dominating.

The outlook with regard to treatment is not as dismal at it would be with the paranoid individual, since paranoid and nonparanoid elements are embodied in separate persons, rather than in the same personality. The hope in the therapeutic program depends on that segment of the population which is nonconforming to the dominant cultural attitude. The first step in treatment would be the immediate identification of conformers and nonconformers, with the disposal of the former so as to prevent their having any kind of power or influence. This would mean putting to death the conformist leaders

and isolation and supervision of the large body remaining. An essential step in the program of long term treatment would be the establishment of the nonconforming segment of the population in power and political influence. Reculturization, the replacement of old ways of thinking and old institutions by new ones; and a general atmosphere of freedom from paranoid values are therapeutic measures of importance. In education the aim would be to substitute Germans who could think objectively and rationally about Germany or any other subject for those of the older education, who were taught primarily the glorification of Germany. This principle and aim should permeate and guide the teaching of all the subjects of the curriculum, especially history, geography and anthropology. Adult education of a similar nature, through the agencies of press, screen, radio, stage, meetings and the children, would be equally important. The elimination of the old pattern of domestic hierarchy under the harsh and dominant father would be one of the aims of the educative process. The small army left remaining would have to be totally reorganized to put an end to the Prussian system of military caste and prestige. The same need would apply to the police force.

The authors recognize that the aforeoutlined measures could be applied only in the framework of new political and economic organization, but they feel that the latter would be futile without the employment of plans of the type they describe.

CHODOFF, Langley Field, Va.

PROLONGED CASE OF GRIEF REACTION TREATED BY ELECTRIC SHOCK. ABRAHAM MYERSON, New England J. Med. **230**:255 (March 2) 1944.

Myerson reports on 4 female patients suffering from "grief reaction" after the death of a husband or child. The symptoms were severe and prolonged, and psychotherapy was tried, without success. One patient had had a depression four years, and it was necessary to produce amentia by electric shock before further shock treatment could effect abatement of symptoms and return of memory. The other 3 patients, whose loss by death was recent, responded after a few electric shock treatments and achieved adequate reorganization of personality.

Myerson concludes that "physiologic alterations of an unknown type take place, and this is the basis of recovery."

GUTTMAN, Philadelphia.

TYPES OF FEMALE CASTRATION REACTION. EMELINE P. HAYWARD, Psychoanalyt. Quart. **13**:45, 1944.

Women who have oriented their lives around penis envy fall into two main groups—the wish fulfilment type and the revengeful type. The revengeful type lives a barren existence, all her potentialities being directed toward revenging herself on the world for her defect. The wish fulfilment type has acquired a penis equivalent, which frees her to use her intellectual potentialities in a constructive manner. Hayward suggests that the little girl who falls prey to penis envy in the anal-sadistic stage is the one who develops into the revengeful type of woman. This situation is frequently encountered when a little girl has been raised with a brother who is nearly her own age. The girl who develops into the wish fulfilment type of woman becomes preoccupied with penis envy after she has reached the phallic level. Such a woman has had no brothers close to her own age.

PEARSON, Philadelphia.

Diseases of the Brain

ELECTROENCEPHALOGRAPHY IN CHRONIC POST-TRAUMATIC SYNDROMES. MOLLIE E. HEPPENSTALL and DENIS HILL, Lancet **1**:261 (Feb. 27) 1943.

Heppenstall and Hill report 150 cases of post-traumatic syndromes studied by means of electroencephalography. A three channel Grass ink-writing oscillograph was used. The results are tabulated as follows:

Diagnosis	Total Number of Cases	Abnormal Tracings		Abnormal Electroencephalograms		
		No.	%	Diffuse	Focal	With Hyperventilation Only
Posteoncussive syndrome	58	33	57	16	16	1
Post-traumatic epilepsy	29	22	76	9	13	0
Anxiety state	21	10	48	7	1	2
Depressive state	19	8	42	5	2	1
Schizophrenic state	2	0	..	0	0	0
Hysteria	14	3	21	2	0	1
Psychopathy	7	2	29	2	0	0
Organic states	87	55	63	25	29	1
Functional states	63	23	37	16	3	4

The time elapsing since the injury seems to bear no relation to the type of electroencephalogram, but the age at which the injury occurred is important. When the injury occurred before the age of 20 years, 65 per cent of the tracings were abnormal; when it occurred in a patient over 20 years of age, 46 per cent were abnormal. The response to hyperventilation showed abnormalities in 39 per cent of cases in the 20 year group and in 16 per cent of cases in the group over 20 years of age. The period of post-traumatic amnesia was of some significance. When it was less than one hour, 43 per cent of the tracings were abnormal; when it was less than one day, 52 per cent were abnormal, and when it was more than one day, 58 per cent were abnormal. These results are of more significance when the abnormalities are divided into diffuse and focal changes. Of the focal abnormalities, 13 per cent occurred in the first group, 48 per cent in the second group and 55 per cent in the third group.

In 18 of the cases of organic disorders the personal history was abnormal, as compared with 33 cases of the constitutional and reactive states. Of the cases in which the personal history was abnormal, abnormal electroencephalograms were present in 37 per cent, and of the cases in which the personal history was normal, abnormal tracings were obtained in 60 per cent. Focal abnormal records were present in 33 per cent of the cases in which the personal history was abnormal and in 47 per cent of the cases in which the personal history was normal. Of the cases in which a family history of neurosis was obtained, focal abnormalities appeared in 26 per cent and diffuse abnormalities in 74 per cent, and of cases in which the family history was normal, focal abnormalities appeared in 54 per cent and diffuse abnormalities in 46 per cent. The assessment of abnormal family histories was wide and was based on the presence of epilepsy, psychosis, severe neurosis, mental defect and psychopathic personality.

The author maintains that abnormal personal and family histories are not likely to increase the probability of an abnormal electroencephalographic record; but when the electroencephalogram is abnormal, the focal changes are more frequent in cases in which the per-

sonal history is normal and diffuse changes in cases in which the personal history is abnormal. Therefore, diffuse abnormalities in the electroencephalogram in a case of a post-traumatic state do not necessarily indicate the presence of cerebral damage.

SANDERS, Philadelphia.

Peripheral and Cranial Nerves

PIGMENTARY DEGENERATION OF RETINA AND NERVE TYPE OF DEAFNESS. W. A. SIRLES and H. SLAUGHTER, Am. J. Ophth. **26**:961 (Sept.) 1943.

Sirles and Slaughter report 12 cases of retinitis pigmentosa. The patients were examined both subjectively and objectively and were considered to have typical cases of this disease. A careful otolaryngologic history was obtained, and thorough examinations were made, including audiometric tests, of all patients. Of the 12 patients, 6 were deaf, as indicated by the audiograms, and showed the typical nerve type of deafness. Only 4 of these gave a history of impairment of hearing. Three of the 4 patients who gave a history of deafness had noticed this symptom from two to twenty-eight years before they experienced any ocular symptoms. It is suggested that a common defect of the germ plasm is present in the anlage of the inner ear and the retina.

J. A. M. A.

NERVE TRANSPLANTATION. N. I. PROPPER-GRASHCHENKOV, Am. Rev. Soviet Med. **1**:28 (Oct.) 1943.

Propper-Grashchenkov discusses experiments on replacement of defects in peripheral nerves, in particular, the Ignatov method of utilizing human nerves taken from corpses and treated with solution of formaldehyde. Ignatov used corresponding nerves, so that the diameters of the nerves could be matched. During the Finnish war there were 13 cases of transplantation in which the defects were so large that direct contact of the severed nerves was impossible. In 1 case a defect of the sciatic nerve amounted to 12 cm. There were cases of defects of the median, radial and ulnar nerves. Repeated chronaxia examinations were made, and motor and sensory functions of the involved extremities were tested with electrometric instruments. Observations demonstrated that the implanted nerve acted as a dead tissue bridge, thereby assuring the regeneration of the nerve fibers. Usually, when motor and sensory functions are lost, a disturbance takes place in the circulation and perspiration of the extremity. It becomes cyanotic, clammy and often covered with ulcers. Every case of transplantation of the formaldehyde-treated nerve tissue showed improvement in each of these dystrophic processes. The transplantation of human nerves in large peripheral nerve defects accelerates the regeneration and reestablishment of the lost motor, sensory and trophic functions and prevents the wounded from becoming invalids.

J. A. M. A.

ATTEMPTS TO ISOLATE POLIOMYELITIS VIRUS FROM URINE. J. A. TOOMEY, L. A. TISCHER and W. S. TAKACS, J. Pediat. **23**:172 (Aug.) 1943.

Toomey and his collaborators tried to demonstrate the virus of poliomyelitis in the urine of patients with paralysis of the bladder. Their attempt was a failure when the monkey was used as the test animal, even though such specimens were obtained at an optimal time, that is, coincident with the onset of the paralysis. Urine obtained post mortem from the bladders of patients with poliomyelitis was tested for the presence of the virus on eastern cotton rats. These tests also gave negative results.

J. A. M. A.

HERPES ZOSTER OPHTHALMICUS: TWO RARE MANIFESTATIONS. T. G. W. PARRY and G. C. LASZLO, Brit. J. Ophth. **27**:465 (Oct.) 1943.

Parry and Laszlo direct attention to various ophthalmic conditions caused by herpes zoster. A woman aged 52 had had an attack of herpes zoster along the ophthalmic branch of the right fifth nerve six weeks previously. The cornea was not involved, but there was a cutaneous eruption with severe pain. Three and a half weeks after the eruption the patient suddenly lost sight in her right eye. The disorder was diagnosed as acute retrobulbar neuritis. After five weeks the visual acuity of the patient had improved. A man aged 33 had had "shingles" on his chest. Three weeks later he felt giddy and had double vision. Examination revealed paresis of the right abducens nerve. The condition gradually cleared up. The few existing statistics on the late ophthalmic involvements in cases of herpes zoster reveal that they occur in the following order of frequency: iridocyclitis (usually a complication of keratitis), optic neuritis and paralysis of the third, fourth and sixth cranial nerves. Retrobulbar neuritis has not previously been mentioned as a signal of herpes zoster.

J. A. M. A.

LOCALISED NEURITIS OF THE SHOULDER GIRDLE. J. D. SPILLANE, Lancet **2**:532 (Oct. 30) 1943.

Spillane describes 46 cases of localized neuritis of the shoulder girdle, which he divides into two groups: in one, of 26 cases, the disturbance developed while the patients were in the hospital or a convalescent home. All these were recovering from an illness (dysentery, malaria, gunshot wound, local sepsis, typhoid, infective hepatitis, a tuberculous lymph gland of the neck, pharyngitis, lobar pneumonia and cerebrospinal meningitis). In the other 20 cases the men were ill while on duty in the field. In 42 cases the first symptom was sharp pain about the shoulder at localized points. The pain was usually worse at night. In all but 1 case there was no fever. There was no rigidity of the neck or back and no diffuse hyperesthesia, and only in the cases in which the deltoid was affected were there sensory changes. The painful sites were tender, but there were no vasomotor changes. Atrophy was well localized and usually pronounced, often led to much disability and affected chiefly the spinatus, the deltoid, the serratus magnus and the trapezius muscles. The patients were treated with analgesics and physical therapy and rest; but there was little alteration in the course of the illness, and atrophy and weakness persisted in the affected muscles in several patients for seven or eight months.

The illness was distinguished from poliomyelitis by absence of changes in the spinal fluid, by the distribution of the paralysis (peripheral rather than segmental) and by absence of general signs of infection or of diffuse hyperesthesia. The condition was thought not to be brachial neuritis or radiculitis because isolated muscles were involved. In these disorders fibrillation and alteration of reflexes are common, and recovery is the rule.

The cause could not be determined. Patients with a history of direct trauma were not included in the series. Repeated slight trauma, such as carrying a pack or rifle could not be excluded in many cases, but in many

other cases the patients were sedentary in their daily duties.

McCarter, Philadelphia.

Costoclavicular Compression of the Subclavian Artery and Vein: Relation to the Scalenus Anticus Syndrome. M. A. Falconer and G. Weddell, Lancet **2**:539 (Oct. 30) 1943.

Falconer and Weddell found the subclavian vessels to be compressed by the clavicle and the first rib alone in 2 patients, without effect from the scalenus anticus muscle, to a sufficient degree to produce paresthesias in both patients and weakness and vasomotor changes in 1 of them. Pressure by the scalenus anticus muscle on a rudimentary cervical rib, as well as costoclavicular compression, caused similar trouble in a third patient; in another, weakness and wasting alone, with no vascular signs, were produced by a fibrous band extending from a long transverse process of the seventh cervical vertebra to a point on the first rib between the course of the first thoracic nerve root and the subclavian artery.

As an aid in diagnosis the authors used two test maneuvers: hyperextension of the neck and downward and backward bracing of the shoulders, the latter being found more effective. The role of the scalenus muscle was tested by paralyzing it with procaine; later it was cut if the condition was severe enough to warrant operation.

Of 50 "normal" men and 50 "normal" women, several showed evidence of the scalenus anticus syndrome when the test maneuvers were carried out. The authors point out that symptoms arise only when this compression can be evoked with ease. In some instances this may mean that the patient has cold blue hands, with a tendency to chilblains, and others, perhaps actual thromboses or even gangrene.

Patients with mild symptoms were relieved by postural exercises; 1 of the authors' patients ceased to complain after his heavy basic training, with pack carrying, was over. Severe conditions merit surgical exploration. The scalenus anticus muscle may then be carefully stimulated to determine its role in the production of symptoms. If this fails to cause symptoms, the finger may be slipped between the artery and underlying rib and the clavicle above to see whether bracing the shoulders will pinch it. Actual compression of the vessels may thus be seen. If this exists, the authors recommend resection of a small segment of rib beneath the artery to relieve pressure symptoms.

McCarter, Philadelphia.

Treatment, Neurosurgery

Sodium Amytal Narcosis in Treatment of Operational Fatigue in Combat Aircrews. Donald W. Hastings, Bernard C. Glueck and David G. Wright, War Med. **5**:368 (June) 1944.

Operational fatigue is a syndrome composed of emotional illness and fatigue, which occurred in a certain percentage of fundamentally stable combat personnel, usually after twelve to eighteen heavy bombardment missions, which exposed the participants to harrowing experiences, tension, fatigue and lack of sleep.

The patients look pale and fatigued. They are irritable and self accusatory about their irritability. They have difficulty in going to sleep; and when they do, they suffer from vivid and terrifying battle nightmares. They are depressed and retarded and suffer from severe anxiety, tremors and gastric and cardiovascular symptoms.

Because depression played a prominent part in the symptoms, it was thought that modified sodium amytal narcosis might be of benefit, since it was useful in the treatment of manic-depressive psychosis. The period of the narcosis was arbitrarily limited to ninety-six hours, followed by a week of convalescence and then return to full duty.

Follow-up studies two months after narcosis therapy were made on 69 patients. Seventy per cent were performing adequately on full duty, and 25 per cent, on ground duty; 5 per cent still had persistent anxiety symptoms.

Pearson, Philadelphia.

Encephalography, Ventriculography, Roentgenography

Osteomyelitis of the Frontal Bone. Lester A. Brown, Arch. Otolaryng. **39**:485 (June) 1944.

Osteomyelitis of the frontal bone is secondary to acute frontal sinusitis in the majority of cases. Only rarely is the condition secondary to chronic frontal sinusitis because during the course of the infection the frontal bone tends to form its own barrier to the spread of the infection. Occasionally, compound fracture of the plates of the frontal sinus or of the bone beyond the confines of the sinus may lead to osteomyelitis. Another possible cause is infection resulting from operation for acute sinusitis when the external approach is employed. The most common symptom is headache. This may vary in intensity from mild discomfort to excruciating pain. Usually the headache is frontal, but occasionally it may be occipital. High fever is not common. The most suggestive finding on examination is a doughy subperiosteal swelling on one or on both sides of the forehead, extending from the brow toward the hair line. The height of the swelling is usually proportional to the osseous involvement. There is tenderness over the involved sinus and sometimes over the entire forehead. Roentgenographic examination reveals decalcification in the involved area.

Brown reports a series of 10 cases of osteomyelitis of the frontal bone, proved at operation, in which most of the usual complications of the disease occurred. These included, in their order of frequency: epidural abscess, cerebral abscess, meningitis, subdural abscess and subperiosteal abscess. Subdural abscess occurred in 2 cases and was rapidly fatal in both, death apparently being due to medullary compression resulting from rapidly rising intracranial pressure. In all the other cases recovery occurred.

Once the diagnosis of osteomyelitis has been made, treatment resolves itself into (1) the attempt to remove the area of infected bone with an area of good bone around it, (2) the attempt to prevent the spread of the osteomyelitis to the supposedly uninfected bone and (3) the treatment of complications.

Ryan, Medical Corps,
Army of the United States.

Society Transactions

NEW YORK NEUROLOGICAL SOCIETY AND NEW YORK ACADEMY OF MEDICINE, SECTION OF NEUROLOGY AND PSYCHIATRY

CLARENCE P. OBERNDORF, M.D., *President, New York Neurological Society, Presiding*

Joint Meeting, March 14, 1944

Biochemical and Electroencephalographic Changes Associated with Delirium Tremens. DR. MARGARET A. KENNARD, DR. ERNST BUEDING and DR. S. BERNARD WORTIS.

In a preliminary study certain of the changes underlying the symptoms of delirium tremens were investigated. This was done by means of biochemical analysis and electroencephalographic studies of a series of 49 alcoholic patients, 40 of whom had symptoms characteristic of acute delirium tremens. The remaining 9 patients, without delirium tremens, were used as controls.

Biochemical Investigations.—Zuckerkandl (Ueber das Verhältnis der Natrium- zur Chlorausscheidung im Harn: Der Natrium-Chlor-Quotient, *Klin. Wchnschr.* **14**:567, 1935) demonstrated that normal human subjects excrete equivalent amounts of sodium and chloride in the urine. The ratio of chloride to sodium in terms of equivalent weights of these two ions varied from 0.9 to 1.15; in other words, normally the same amounts of sodium and chloride are excreted. In pathologic conditions associated with inflammation of the serous membranes, such as pleurisy, ascites or polyarthritis, Siedek and Zuckerkandl (Ueber das Verhältnis der Natrium-zur Chlorausscheidung im Harn: Der NaCl-Quotient der entzündlichen und kardialen Erkrankungen, *Klin. Wchnschr.* **14**:1137, 1935) reported that there was retention of sodium and that, as a consequence, much less sodium than chloride was excreted in the urine.

Since delirium tremens is associated with a considerable loss of water and salt, the excretion of sodium and chloride in the urine was investigated. Of 19 patients studied so far, 11 showed a chloride-sodium ratio outside the control range of 0.8 to 1.2 on admission. Seven of these 11 patients excreted less chloride than its equivalent of sodium, and for 4 patients the reverse was true. For the 7 patients with low chloride excretion on admission the chloride-sodium ratio returned to normal in one to four days.

The abnormalities in this ratio were often more pronounced for the urine excreted during the four hours after 1.5 liters of water had been given the patient. The return to normal of the chloride-sodium ratio was not preceded by a reversal of this ratio; in other words, there was not an excess of chloride over sodium. This indicates that no retention of chloride or excessive excretion of sodium had existed at the time of admission of these patients. It is more likely that an excessive loss of chloride occurred at this time.

Electroencephalographic Study. — Twenty-three patients with delirium tremens showed a pronounced tendency in all records to wave forms of low amplitude and fast, 20 per second activity. There was in all records a relatively low percentage of 8 to 12 per second activity. The patients who showed least of this alpha activity, of medium rate and low amplitude, were persons whose history and occupation indicated deterioration, although their symptoms in the acute attack were no more severe than the symptoms of patients with more nearly normal patterns of cerebral activity.

It was also found that the patients who had the highest percentage of alpha activity on admission were those who recovered most rapidly. For all patients with clinical recovery there was an increase in the percentage of alpha activity in the record. But this increase was less pronounced in the records of the "deteriorated" patients which showed originally the greatest deviation from the normal pattern.

Phlebothrombosis and Phlebostasis of the Brain in the Newborn and in Early Childhood. DR. OTTO MARBURG and DR. LOUIS CASAMAJOR.

This paper was published in full in a previous issue of the ARCHIVES (**52**:170 [Sept.] 1944).

DISCUSSION

DR. TRACY J. PUTNAM: Dr. Marburg deserves to be commended for avoiding the error which is all too common in neuropathology of leaping abruptly from the clinical picture or the gross pathologic changes to the ultimate etiologic factors. It is seldom one can make this leap. One must usually move step by step from what is observed at autopsy to the point where the chain of evidence begins for practical purposes. It is gratifying that Dr. Marburg has analyzed these lesions in terms of damage to or disturbance of the venous drainage, for another shortcoming of classic neurology is its neglect of the venous system. The pathologist studying Weigert preparations is apt to regard the vascular system as being merely ancillary to the nerve structures, when actually it is the other way around —the nerve structures are entirely dependent on their circulation. Moreover, while the term "vascular injury" is extremely common in neuropathology, and the general outlines of the results of disturbances in the vascular supply have been familiar since the days of Wepfer, vascular injury practically always means arterial thrombosis. This was well shown by Hassin, for example, in his discussion on the possible vascular origin of the lesions of multiple sclerosis. He said such lesions had nothing to do with the disposition of the arteries of the nervous system and dismissed the whole matter, as others have done.

The lesions which Dr. Marburg presented have been well described before. It has not been clearly recognized that such lesions, and others of this type, are within reasonable limits to be interpreted as the result of disturbance in the venous circulation. It is not difficult to see how this error came about. First, the classic neuropathologic stains successfully concealed the vascular system. That is what they were for. They were intended to stain the nerve elements, and usually not the mesodermal elements, and they were apt to

conceal the content of the blood vessels. Second, the damage takes place rapidly, without any question. Once a thrombus or any other type of obstruction forms in a vein the damage to the parenchyma takes place in a few hours. It is there to stay; the actual nerve elements never regenerate, and the subsequent events consist in the formation of a scar. By the time the scar is well formed the thrombi may have disappeared entirely; so it is fortunate that Professor Marburg encountered the telltale thrombi in the proper place in some of the lesions. I take it that some of the lesions he studied had already passed the stage at which thrombi could be seen. In any city under bombardment there are always more burns and ruins than there are fires in progress, but one usually concludes from the ruin that there has been a fire; so with these lesions, one must study a series before concluding that the scar must have resulted from this type of injury, and not from any other. From the injury, one can then pass to the next step in the progress of the formation of the lesion. As to whether or not the injury is always trauma in cases of this kind I am not wholly convinced. I believe I have seen a case much like Dr. Casamajor's second case in which the lesion was already in the scarred stage within a week after birth. The acute process must therefore have occurred before birth. This may have been one of the cases which Professor Marburg mentioned in which the lesions occurred as the result of injury during fetal life. I think this study represents an important addition to the series of pathologic pictures which begins with the birth injuries and passes through diffuse sclerosis and so into multiple sclerosis and the encephalitides; all these processes may or may not be due to the so-called inflammatory phenomena, which are seen about as often in cases in which the origin was obviously traumatic as in cases in which infection may conceivably have played a part. .

Professor Marburg has performed a great service in again calling to attention the extraordinary prevalence of birth injuries, a subject the gravity of which is well recognized by obstetricians, neurologists and psychiatrists. The unfortunate victims are usually swept out of the broader currents of daily life and collect in the backwaters of institutions, and so are less often seen. It is important, however, to remind oneself of their existence and to keep struggling with the problem of how such cases may be prevented. It is clear that such conditions as have been presented tonight can scarcely be cured and that surgical intervention would not in the least be helpful to any patient of this group. Whether chemical or biologic means may be found to prevent such lesions is an important study for the future. I wish to compliment the authors for pointing out the cardinal features of this syndrome and its human and economic importance.

DR. JOSEPH H. GLOBUS: I am glad Dr. Marburg reopened the question of porencephaly. Indeed, he did not use the term "porencephaly," but the designation can well be used to describe the pathologic picture in the cases presented tonight. The brain showed numerous extremely large cavities, in accordance with the classification of porencephaly.

I hoped that Dr. Marburg would recall a case which I presented about twenty-two years ago in which the dissolution of brain tissue which led to the cavity formation was due to interference with the blood supply. At that time it was my opinion that the interference with the blood supply was the result of strangulation of the blood vessels by thickened meninges in the region of their penetration into the cerebral cortex. I was able to demonstrate the presence of actual scar tissue at this point. The vessels in their course were collapsed and empty. In this way, I thought, I have shown that the dissolution of brain tissue is the result of interference with the blood supply, and this, in turn, is the result of strangulation of blood vessels.

Dr. Marburg has given important support to my concept by demonstrating that the interference with the venous supply was responsible for the pathologic process in his cases.

DR. OTTO MARBURG: In reply to Dr. Globus' comment on porencephaly, we did not use this term in our case because porencephaly means the presence of cavities in the brain substance communicating with the lateral ventricles. There must be an open connection between the cavities and the ventricles.

DR. LOUIS CASAMAJOR: I am afraid Dr. Putnam misunderstood what I said. The second patient did not show the condition immediately after birth. The child was apparently normal at birth, and the obstetrician told the parents that the baby was normal; he seemed normal, except that they were unable to find any satisfactory formula. Nothing abnormal was noted until two and a half months after birth, when the left foot became spastic. The opisthotonos did not appear until four or five months after birth, and from then on the retraction of the head increased until it reached the position seen in the illustrations. I had difficulty in thinking of this condition as congenital, and until Dr. Marburg went over the sections and offered me this theory of phlebothrombosis, I was at a loss to understand why the condition was progressive. The child was 1 year old before I saw him. I knew nothing about the case before that except for the history, which was that of a progressive condition.

DR. H. A. RILEY: Is it Dr. Casamajor's belief that this child had a normal brain when it was born and that the situation seen at autopsy developed after birth?

DR. LOUIS CASAMAJOR: I do not know. The child was said to be normal; I believe that when he was born he did not have the kind of a brain he had when he died. The brain may not have been normal at birth, but I believe it was not as degenerated as it was at death. If it had been, I cannot see why the child was 4 or 5 months old before retraction of his head became apparent, after which the opisthotonos progressed until the vertebral column was a hoop. I believe this was a progressive condition, and not congenital at all.

Prognostic Significance of Certain Factors in Schizophrenia. DR. NOLAN D. C. LEWIS.

The modern psychology of schizophrenia has been constructed on the basis of concepts of Kraepelin, Bleuler, Freud, Jung and their immediate derivatives or schools of thought. Kraepelin's work is well known, as is that of Bleuler, who approached the problem from the standpoint of an organically determined change in the associations. His main contribution lies in the painstaking evidence he compiled on the psychologic determination of the majority of schizophrenic manifestations. Jung, studying the problems from his psychologic point of view, concluded that the psychic symptoms were not dependent primarily on disturbances in association. For example, he interpreted schizophrenic negativism as an attitude of rejection, and not as a consequence of interruption in associative processes. Freud's theory of schizophrenia rests basically on the concept of regression from object relations to the state designated as "narcissism."

A better understanding of schizophrenic psychology may be revealed by more complete studies of patients treated with insulin or convulsive shock methods. There is no known pathogenesis of schizophrenia as an entity. Therefore one must consider each subtype separately, an approach which is reenforced by Birnbaum's structure analyses, Kretschmer's multidimensional diagnostics, Bleuler's *Tiefenpsychologie* and other systems of analysis.

There are many blunders in the diagnosis of the schizophrenias, and a better understanding may be effected by carefully organized studies of the outcome.

The pathogenesis and diagnosis of schizophrenia are actively disputed factors, a fact which renders prognosis difficult.

The great diversity in the symptoms, as seen and described in psychiatric clinics and assembled under the diagnosis of schizophrenia, is difficult to explain unless a large number of contributing factors and combinations is assumed.

There is evidence of a central type of schizophrenia, with other, marginal, forms, which may be termed "symptomatic" schizophrenia, and certain acute exogenously determined psychoses. However, one must have proof of the relation of exogenous injury, infections, prepsychotic personality traits and hereditary components before utilizing etiologic factors as a basis for prognosis. Clinically it is advantageous to separate atypical schizophrenic conditions from the main forms and give them an identifying description.

Although it is not the purpose of this paper to discuss shock therapy in any detail, in the present era, which might be designated as one of shock methods, its relation to prognosis should be one of the first considerations. The discordance in the opinions of recognized experts in the field, based chiefly on inadequate, or at least dissimilar, research procedures, has left me, and probably others, without any answer to the following questions: Does shock therapy cure patients otherwise incurable, or only shorten the duration of a schizophrenic illness bearing a favorable prognosis? Is shock therapy the deciding factor in the recovery of patients for whom the prognosis is doubtful? How lasting are the results? Are they more or less permanent than spontaneous or psychotherapeutic recovery? Does shock therapy harm the patient? All patients? Or only certain types of patients?

Kretschmer emphasized that the weak leptosome, with asthenic body build, is highly predisposed to the schizophrenic process and that the pyknic body form is in some way antagonistic to this type of mental disorder. Manz found that catatonic features are more frequent in persons of athletic build and that they tend to favorable remissions. Hebephrenic forms are more frequent in persons of dysplastic habitus. Here there is a tendency to primitive reactions and naïve spontaneous expressions of emotion as dominant features in the prepsychotic character, with exaggerations of these features in the full blown psychosis. For the majority of persons of this type the prognosis is poor, as it is for persons of another special group, with asthenic body build. These patients are highly educated, prepsychotically introverted, hyperesthetic persons—teachers, students of religions and of philosophy, often with interests in reform, who progress rather rapidly to deterioration.

Schizophreniform or atypical schizophrenic attacks in imbeciles are recoverable. There is a question whether such persons are really schizophrenic. When a "nuclear" schizophrenia appears in a feebleminded person, early deterioration may be expected. However, in many persons of a low order of intelligence there develop schizophreniform reactions which have a good prognosis, and, as mentioned before, these reactions probably belong in a separate pattern category.

While isolation of symptoms from a pattern for special consideration is always controversial, certain combinations are of prognostic importance in this respect.

Kraepelin, Stransky, Meyer and many, more recent, investigators have observed that the acute occurrence of catatonic forms carries a favorable prognosis, but Bleuler found that schizophrenias in which the catatonic features appeared gradually had an unfavorable prognosis. Kraepelin pointed out that the condition of deep stupor and of severe catatonic excitement had a favorable outcome; however, semistuporous states with continued stereotypy in the quiet periods have a bad significance. It is the experience of most psychiatrists that the majority of patients who have passed through a severe catatonic psychosis will carry the marks of it through life, even though they are independent and socially adjusted.

Some paranoid ideas can be regarded as temporary compensatory symptoms, and therefore not "nuclear." Ideas of persecution and poisoning in a moderate degree have little unfavorable significance. In fact, some self-reference tendencies and vague symptoms of splitting tend toward a cure, or a cure with a remaining defect. However, it is realized that massive paranoid developments are fixed and resistant to therapy.

It is important to know, for diagnostic and prognostic reasons, as much as possible about the following features of a given case:

1. The influence of prepsychotic factors
   - (*a*) Heredity
   - (*b*) Morphologic type
   - (*c*) Prepsychotic character
   - (*d*) Social factors
   - (*e*) Intellectual foundations
   - (*f*) Prepsychotic physical and mental traumas
2. Initial stage of psychosis
   - (*a*) Age of onset
   - (*b*) Onset, insidious or sudden
   - (*c*) Exogenous precipitating factors
3. Symptoms of acute stage of psychosis
   - (*a*) Abundance or poverty
   - (*b*) Type of symptom pattern
4. Course of the disorder
   - (*a*) Steadily or gradually progressive from the beginning
   - (*b*) Form of "attack"—tendency to remission
   - (*c*) Catastrophic development
5. Physical disease components.

Studies following these lines of investigation have shown that certain combinations of factors in an essentially schizophrenic psychosis favor a good prognosis, while others indicate a poor prognosis, regardless of the type of general or special treatment afforded. Some combinations with a favorable prognosis are: pyknic habitus and cycloid temperament plus a presenting affect in the psychosis (particularly a depression); pyknic habitus plus cycloid temperament plus active exogenous precipitating factors, and athletic habitus plus schizoid temperament plus exogenous precipitating factors and amnesia for the acute phase.

Asthenic habitus plus schizoid temperament carries an unfavorable prognosis. asthenic habitus plus cycloid temperament means usually an unfavorable prognosis. The prognosis for children with schizophrenic-like personality and poor abilities is usually poor, as it is as a

rule for "clever" children with a schizoid temperament. Special abilities do not seem to help much.

There is evidence that persons with atypical forms of schizophrenia, or pseudoschizophrenic types, as they have been called, form a large percentage of the patients in various clinics and outpatient departments whose disease is diagnosed as schizophrenia or dementia precox. It is possible, if not probable, that herein lies the cause of the differences in reported therapeutic results, which are far more favorable for the pseudoschizophrenic than for the "nuclear," or genuine, form.

When the diagnosis is simply "schizophrenia," or dementia precox, a statement that 50 to 60 per cent of patients were cured or improved gives inadequate information concerning the relation of cure to therapy. Psychiatrists are in a clinical position to demand complete and accurate information as to the form of schizophrenia present. Only careful studies and precise statements will justify interhospital cooperation in a solution of the problems of schizophrenia.

DISCUSSION

DR. JAMES H. WALL, White Plains, N. Y.: Dr. Lewis has brought together some interesting points for consideration. In my experience, a significant factor in a good prognosis for a schizophrenic illness is a mature and evenly balanced personality. Often this is associated with more vigorous physical health. The more adequate the precipitating causes, the better the outlook. The preservation of the emotional attitude, of fighting off and not accepting the illness, no matter how deep the regression, is a good sign. The attitude of the relatives of schizophrenic persons plays an important role. Many of the patients who recover and improve to a notable degree are surrounded by mature, flexible and tolerant personalities in their families. So frequently the chance of restoration is interfered with by relatives who are inflexible and unteachable, and in their emotional thinking know more than trained psychiatric workers about what is best for the patient before, during and after the acute phase of the illness.

DR. PAUL FEDERN: I have only a few words to say about the impressive paper by Dr. Lewis, whose all-embracing experience covers the most varied cases. He was careful to follow up all the many factors of importance with cautious statistics. He demonstrated that there are a few conditions which allow one to expect a better than average course of the disease. Yet in the main a combination of factors is necessary to justify a good or a bad prognosis; a few specific combinations condition even an optimistic prognosis. I do not disagree with any statement of Dr. Lewis.

However, the psychiatric specialist, and even the head of a clinic, see cases of more advanced disease; rarely do his observation and his therapy begin early enough to influence the course of the illness from the beginning. For this reason, the prognosis with regard to psychotherapy, and especially psychoanalytic therapy, becomes different when based on experiences of the family physician or the practical psychoanalyst. One usually sees patients with early psychosis because of an error of diagnosis, but one can observe complicating factors from the beginning. By recognizing schizophrenia in the state of preliminary neurosis or when the first false conception of reality appears, one can treat and protect the patient in an early phase. I am convinced that such early diagnosis and treatment will influence the course and the prognosis.

One might learn to make the diagnosis even before false reality of thoughts and mixing of reality and unreality are established. Yet the patient is already aware of difficulty in maintaining the differentiation of thought and reality; the conception of reality temporarily ceases to be automatic; temporary and partial estrangement is felt. Sometimes the patient can overcome these disturbances by active attention; usually there is abnormal fatigue as the consequence of such attentiveness. I do not know what percentage of cases begins in this way. Also, I could not say that neurotic and prepsychotic estrangement are symptomatically different. Yet I have had patients remain in the stage of estrangement for twelve years.

The early phase of schizophrenia can be compared with the early beginning of tuberculosis in childhood. Since the protection and treatment of patients with early disease, the statistical aspect of tuberculosis has changed. Learning difficulties and behavior changes may be the first disturbance in schizophrenia; if one learns to recognize such first symptoms, the prognosis will improve. Meanwhile Dr. Lewis is to be thanked for having directed attention again to the multiple conditions of the developed process.

DR. JOHN G. LYNN: It is gratifying to have Dr. Lewis present in such a clear manner this outline of factors which seem to operate in the prognosis of schizophrenia. With reservations incidental to my own, more limited, psychiatric experience, I should like to mention a factor which, in my opinion, is of importance as an indicator of the prognosis and which I do not believe has been noted.

At McLean Hospital, Waverley, Mass., I noted that the schizophrenic patients who had had strongly developed visual orientation since early childhood, who manifested interest in manual and concrete activities in association with a lack of interest in verbal and auditory activities, seemed to have a better prognosis for recovery. Many of them were mechanically inclined, or they liked to draw or paint. In contrast, the schizophrenic patients who gave a history from early childhood of having a more auditory-verbal orientation, to the detriment of their visual and concrete interest, carried a poor prognosis and showed more rapid deterioration. The latter patients usually gave a history of being superior in languages and of having had musical interests, in preference to painting, drawing, sculpture or mechanical activities. Because of their predominant auditory-verbal orientation, it seemed easier for them to split off their abstract verbal levels from their concrete visual levels of thinking. As a consequence, any discrepancies between the content of their abstract verbal level and the content of concrete visual level of perception was not so noticeable or disturbing to them. In fact, their abstract verbal level seemed to operate, in an omnipotent way, almost entirely as an agent of wishful thinking, relatively free from the normal necessity of contemporaneously maintaining some degree of structural or factual correspondence with concrete visual reality.

Did Dr. Lewis observe that a more concrete visual orientation was a good prognostic sign, and a more auditory-verbal orientation a poor prognostic sign, in schizophrenia?

DR. NOLAN D. C. LEWIS: My paper is composed chiefly of conclusions. It should follow the evidence which led to these conclusions. The material on which my studies were based consists of more than 1,000 cases, and the impressions presented here were based on a series of 600 cases. The material when published in full will contain this evidence.

Dr. Lynn stated in language that one can understand his impressions of the prognosis for patients with a strongly developed visual orientation. It has always seemed that such persons have a greater diversity of interests than those who are interested in, and who think characteristically in terms of, abstract processes. It is recognized that the presence of visual hallucinations in a case of schizophrenia is usually a favorable prognostic sign. It often indicates an active toxic element in the situation, while the common auditory hallucinations are more malignant and more characteristic of the nuclear, or central, type of schizophrenia. Many of the persons who break down are those who spend a great deal of their time in a more circumscribed environment, in a self-imposed isolation, where they build up a world of their own, and if they avoid a full blown schizophrenia and get started along lines of creative thinking, they may become efficient librarians or college professors. Certain of the expressions or symptoms of schizophrenia act as a healing process to save the patient from regressing too far or becoming completely dissociated, and thus are constructive forces. Many patients struggle to hang on to reality as long as they can before slipping into a deep psychosis. Symptoms may represent healing tendencies, and if one knew in the early stages how to time the therapy just right, or which symptoms to support as aids to healing, one might help greatly in the correction of the disorder. As in other pathologic processes, when some of the somatic pathology is an attempt of the tissue to repair damage, one should attempt to promote any action which preserves the healing tendency.

PHILADELPHIA NEUROLOGICAL SOCIETY

GEORGE D. GAMMON, M.D., *Presiding*

Regular Meeting, March 24, 1944

Intelligence Following Prefrontal Lobotomy in Obsessive Tension States. DR. JAMES W. WATTS and DR. WALTER FREEMAN.

In 1938 we reported on the results of interruption of the frontal association pathways in 6 patients with obsessive tension states. We have continued our studies on these and similar patients, and now we can amplify our conclusions, based on 45 patients studied from one to seven years after operation.

Prefrontal lobotomy relieves nervous tension and obsessive thinking. After operation the patient may still cling to the idea that he has tuberculosis or syphilis or that his eustachian tube is stopped up. A woman may look in the mirror and see just as much hair on her face and arms as before operation, when she thought that suicide was the only solution. But if the idea no longer is accompanied by a heavy emotional charge, it loses its importance and no longer dominates the patient's life.

In the 45 patients under discussion, it was the emotional charge, therefore, that caused the disability, rather than the peculiar ideas themselves. Furthermore, there was no significant deterioration, either intellectual or emotional. Although the average duration of symptoms of these patients was slightly more than ten years, only 5 had been confined to hospitals for mental disease.

If brain-damaging therapeutics is to be employed for patients without mental deterioration, it is important to know how the intelligence is affected by the procedure. If relief of mental pain is secured only by sacrifice of the intelligence and understanding, the price is too great.

According to the "Encyclopedia Britannica," "Intelligence of understanding is a term that is still used by psychologists with considerable latitude of meaning. Sometimes it is used as a synonym of 'cognition,' that is to say, it is applied to any of the numerous processes by which knowledge is built up. Sometimes it is restricted to the conceptual process, as distinct from the process of sense perception. Some [psychologists] frankly admit that they do not know and do not care what this 'intelligence' may be which they are measuring, so long as these measurements can be made use of. Lastly, ordinary everyday usage perhaps tends to emphasize the practical character of intelligence as consisting in the ability to employ the right means in order to achieve the various ends pursued."

In this paper, we are concerned with the practical character of intelligence, and if our yardstick of intelligence is "the ability to employ the right means to achieve the ends pursued," then it would appear that our patients are more intelligent after lobotomy than before. Before operation, only 17 per cent were leading useful lives; 13 per cent were employed; 2 per cent were employed part time and 2 per cent were housekeeping. At present, 67 per cent are leading useful lives; 38 per cent are employed; 11 per cent are employed part time, and 18 per cent are housekeeping. The statement does not imply that the patients are restored entirely to normal, for many show personality changes indicative of frontal lobe deficit, but 67 per cent are now employing their ability in a manner to achieve the ends pursued, as compared with 17 per cent prior to operation.

Persons with obsessive tension states have energy and ambition; they are meticulous, economical and punctual. While they may not always be agreeable, they are good workers and often find that their old positions have been held open for them if they have not been away too long. On returning to work, they are usually slow for a while, but accurate, and perform their duties to the satisfaction of the employer. Most of the patients seek work in the same type of employment in which they had been engaged before lobotomy. A few may change occupations, like a clerk in the Treasury Department, who had never liked anything about his job except getting his pay check twice a month. Radio had always been his hobby, and after operation, still finding work in the Treasury Department obnoxious, he resigned and became a radio operator. At present he is teaching the mathematics of radio in the Signal Corps.

Patients in this group come seeking lobotomy, in contrast to patients with involutional depressions, who are virtually dragged in by their relatives. They believe that if they can be freed of nervous tension they can apply themselves to their tasks and reach their goals. Prefrontal lobotomy relieves nervous tension and often aids the patient in achieving the end he pursues. For persons who have set their goal too high, lobotomy brings it closer, but does so by making them more easily satisfied with their accomplishments. It makes them willing to do work commensurate with their abilities.

DISCUSSION

LIEUT. PAUL J. SCHRADER: I agree with Dr. Watts and Dr. Freeman in their observations on the intelligence after lobotomy. My colleagues and I have now checked the intelligence of about three fourths of all the patients on whom we have operated, and, so far as I know, intelligence is not significantly disturbed.

We have no preoperative standard. These patients do surprisingly well after operation, even the schizophrenic group. There were 208 patients, of whom about 88 per cent were schizophrenic with institutional practice. I continue to be astounded by the letters I get from relatives, who say, "Well, John is working now. John is doing well." Well, I know that John had been in the state hospital for several years. What is intelligence? If it is the functional capacity, then on the whole prefrontal lobotomy does not disturb it. However, the worst, I should say the most unfortunate, results were in the obsessive group with tensions.

A professor of a midwestern university had a conceit which he was able to hide from his family; after operation he had complete loss of social sense, and we had to commit him to an institution. In our entire series of patients his was the only unfavorable result. Yet his intelligence was undiminished. His social sense was, I should say, lost. The operation had not aided him, but the results with the obsessive tension states were impressive. I believe that the procedure is about as specific a treatment as can be given for these obsessive tension states.

I am entirely in accord with Dr. Freeman and Dr. Watts in their statement that, judging by all means now available, intelligence itself is not diminished by prefrontal lobotomy.

DR. HERBERT FREED: The authors spoke of a patient who had psychoanalysis and reported their experience with other patients. How many of them try intensive psychotherapy after operation, and how do they take it? Do they seem to gain insight into their obsession with intensive psychotherapy? Do the authors use it? Do they advocate its use after the lobotomy?

DR. WALTER FREEMAN: In answer to Dr. Freed's question, I know of only 1 patient who had psychoanalysis after operation. Five had a rather formal psychoanalysis before operation, the periods ranging from eight months up. One man had fifteen months of psychoanalysis before operation, without any significant progress. A young woman had had psychoanalysis before lobotomy, without any progress at all.

The reaction of the patients to postoperative psychotherapy is not good because they are so free or so devoid of all introversial feelings and of all interest in themselves. It is practically impossible to get them to pay attention to their various mechanisms. Lobotomy makes introspection especially difficult. These patients would rather talk about the weather, what they are going to do or where they are going to go. Their attention is devoted to outward manifestations, and they seem not to like to discuss their symptoms any more.

DR. FRANCIS C. GRANT: I have had no experience with lobotomy in treatment of the obsessive and ruminative states. The largest number of patients on whom I have operated had a manic-depressive psychosis. For these patients lobotomy was effective, although, seemingly, as much now can be accomplished by electric shock therapy. Recently I have had the opportunity of operating on a number of schizophrenic patients. The results have varied directly with the mentality of the patient prior to operation. If the patient was violent and mentally dilapidated before operation, his violent attacks will in great measure disappear after operation, and the amount of useful intelligence he has may seemingly increase. But he will never have a normal intelligence. Unquestionably, in my experience, lobotomy blunts the intelligence. After operation the patient may seem more active mentally, but that is because lobotomy enables him to make better use of what he has left.

DR. RUDOLPH JAEGER: I wonder if there is any reason for arguing whether or not the intelligence of these persons is increased by lobotomy. It is a matter of whether or not the intelligence that they have can be made to work. For example, one youngster with catatonic dementia precox on whom I had operated had been in hospitals for psychopathic patients for many years. He was absolutely useless and had to have constant nursing attention. Since the operation he has been able to work in a pawnshop and has carried on now for three years, doing first-class work. Now one might say this patient had more potential intelligence before he was operated on and that the lobotomy may have reduced this intelligence, if there were accurate methods of measuring his brain capacity, but certainly he was not using his intelligence for any practical purpose. No matter how intelligent a person, if that intelligence is not properly used it is of no practical value. This is certainly true of most of the patients with obsessive tension. I have had only a small number of patients, perhaps not enough even to comment on the results.

I have had only 10 patients with mental disease on whom operation was performed prior to a year ago. The oldest patient, operated on more than three years ago, had an obsessive tension state. She was forced on me by my friend, Dr. Walter Freeman, and her family. Her condition has greatly improved, and she has gone back to her home and is able to carry on her household duties as a capable wife. Before the operation she was a total loss to her family. She may have been ever so intelligent, but certainly she was not using her intelligence to any degree of efficiency.

Of my 10 patients on whom prefrontal lobotomy was done, 6 had obsessive tension states. One of these 6 died of senile complications three months after the operative procedure. One of them showed no improvement. Four could be called almost completely cured. All of them had had shock therapy and prolonged treatment in hospitals for psychopathic patients. The 4 cured patients were among the first I had, and their improvement was remarkable. There were 4 patients with schizophrenia in my series. Three of them were greatly benefited, and 1 failed to improve. I have a great deal of enthusiasm for prefrontal lobotomy in selected cases of mental disease. The improvement following operation is a thing one cannot overlook when one compares the condition before and after the procedure.

DR. JAMES W. WATTS: Among the numerous definitions of intelligence, we have chosen as a yardstick "the ability to employ the right means in order to achieve the various ends pursued," and we have emphasized its practical character. If one uses a different definition of intelligence, then one might arrive at a different conclusion.

In answer to Dr. Grant's question, I believe it is more difficult to arrive at a conclusion about intelligence in schizophrenic patients, as there is a tendency for many of them to deteriorate. If they do deteriorate, it is difficult to say whether deterioration is due to the disease or to the operation. Patients with obsessive tension states are better material for study of this problem; our patients rarely showed evidence of deterioration, even though the average duration of symptoms was ten years.

Electroencephalographic and Pneumoencephalographic Studies of Multiple Sclerosis. Dr. Walter Freeman and Dr. Robert Cohn, Washington, D. C.

Fifteen cases of multiple sclerosis have been studied by pneumoencephalography and 6 cases by electroencephalography, 4 of the 15 cases being studied by a combination of the two methods. The pneumoencephalographic findings consist of asymmetric dilatation of the ventricles and irregular stellate shadows and large striations over the surface of the brain, occasionally symmetrically located. A characteristic position is the medial aspect of the hemisphere. Increased air in the posterior fossa, especially around the pons, is seen in some cases; the fourth ventricle may be dilated and the cerebellar folia show up prominently. Encephalograms made at intervals may show increased enlargement of these air shadows, particularly in the third ventricle. In some cases of long duration of the disease the changes are minimal.

The electroencephalogram was abnormal during an acute exacerbation in only 1 case, and as the condition went on to remission the electroencephalogram also became normal.

Autopsy was performed in 4 cases, and comparison of the photographs of the brain with the roentgenogram shows a fair degree of correlation of the shadows with the sinking in of the cortex due to destruction and cicatricial contraction of the subcortical white matter. Histologic study of the brains indicated that the pathologic process in disseminated sclerosis may destroy with relative completeness the subcortical white matter and yet leave the cortex almost entirely unaffected except for the radial fibers.

It is concluded that the pneumoencephalographic findings are due not to local cortical atrophy but to sinking in of the cortex following cicatricial contraction of the subcortical white matter, and that the electroencephalogram, which is normal, shows a high correlation with the preservation of architecture of the cerebral cortex.

DISCUSSION

Dr. Michael Scott: In 1936 I presented at a meeting of this society (Arch. Neurol. & Psychiat. **38**: 218 [July] 1937) 6 cases of multiple sclerosis in which the encephalographic changes were practically identical with those described by Dr. Freeman tonight. The roentgenograms showed predominantly dilatation of the ventricular system and increased sulcus markings in the frontal lobe, in the parietal lobe especially and in the cerebellum. In all these cases large amounts of cerebrospinal fluid, often in excess of 200 cc., were removed at the time of the air studies.

Dr. Samuel B. Hadden: Dr. Scott's mention of his cases has refreshed my memory. I think he will recall that in discussion of his presentation I showed roentgenograms in cases of a condition clinically diagnosed as cerebellar ataxia; in these cases the findings were much the same as in Dr. Scott's cases and in those which Dr. Freeman presented tonight.

Dr. Matthew Moore: Dr. Freeman's contribution is important, it seems to me, because he has again demonstrated that by means of pneumoencephalographic studies one can correlate intravitam cerebral changes with gross postmortem observations, rather than because of his intimation that multiple sclerosis has a specific encephalogram.

In 1934-1935 I presented a series of 152 cases of various types of psychoses, of both organic and nonorganic origin, in which pneumoencephalographic studies had been made. Among these were many instances of schizophrenia, epilepsy and early dementia paralytica in which the cortical atrophies were similar in many respects to the changes Dr. Freeman has shown. With dementia paralytica, there is supposedly a characteristic pneumoencephalogram. However, this is not entirely true, as there are essentially two types: one showing intense, spotty cortical atrophy with dilatation of the ventricular system, and the other presenting the so-called ground-glass appearance of the hemisphere with pronounced symmetric or asymmetric dilatation of the lateral ventricles. I do not believe that a specific pattern exists with multiple sclerosis or Freidreich's ataxia, as has been suggested by Dr. Hadden, and it would be difficult indeed, without clinical data, to make a definitive diagnosis on the basis of the pneumoencephalogram alone. The results of air studies can be interpreted only as a reflection of the changes occurring within the cortex or subcortex, with the secondary manifestations in the configuration of the surface of the brain and the ventriclular system resulting from atrophies and contraction of the tissue.

Dr. N. W. Winkelman: Dr. Freeman has portrayed vividly the recognized underlying morbid process in multiple sclerosis. One could have surmised that there may be ventricular inequality, and at times dilatation, for one of the characteristics of multiple sclerosis is the periventricular location of the characteristic patches of sclerosis. It is also known that the morbid process is as a rule located beneath the cortical gray matter, and not within it. The complete disappearance of the myelin sheaths from one area of the subcortex with preservation of the U fibers, shown in one of the slides, is unusual in a case of multiple sclerosis. It is more commonly seen with other demyelinating diseases, such as Schilder's.

Knowing, therefore, that the morbid process of multiple sclerosis is subcortical, and not cortical, one is not surprised to learn that there is little or no change in the electroencephalogram. One could not, therefore, make a diagnosis of multiple sclerosis on the basis of the brain wave pattern.

Dr. Walter Freeman, Washington, D. C.: In the last case, in which the subcortical tissue was apparently so devastated, an encephalographic examination was not made. I do not know why the electroencephalogram is normal in cases with destruction of areas of the subcortical tissues and with the slot effect in the encephalogram, unless it is that the cortex is anatomically intact. The cell bodies themselves and the intracortical connections apparently keep up this wave pattern through the cortex.

Is the encephalogram specific for multiple sclerosis? I do not think so. It is only suggestive of the disease. My associates and I have made a diagnosis of multiple sclerosis in 2 cases of an obscure condition by finding such stellate shadows over the cortex. I am willing to grant that Friedreich's ataxia causes atrophy of the cerebellum. I am interested to hear that the atrophy also involves the parietal area in this disease, for I have not observed it. Even so, I should expect the air, or the atrophy, whichever one prefers to call it, to be symmetrically distributed over the cortex in cases of Friedreich's ataxia, whereas asymmetry is the rule with multiple sclerosis.

In cases of dementia paralytica there is another complication, for the meningeal infiltration may cause loculation of the air and variable filling of the subarachnoid spaces. That does not often happen in cases of multiple sclerosis, although it did occur in 1 or 2 cases of the

series. With dementia paralytica there is usually dilatation of the ventricles, but my experience has not been large.

Neonatal Toxoplasmosis. Dr. N. W. Winkelman and Dr. Matthew T. Moore.

Human infection with Toxoplasma hominis has recently created interest because of an increasing awareness that this condition is probably more prevalent than the relatively small number of cases recorded in the literature would indicate.

In the infantile form, manifested chiefly as encephalitis or meningoencephalomyelitis, there is increasing evidence that the infection is of antenatal origin and that it is transmitted to the fetus via the mother. It is not unlikely that some stillbirths and deaths of 1 or 2 day old infants have been due to unrecognized toxoplasmic encephalitis. Although the cerebral lesions may be severe and extensive, some patients survive beyond infancy.

Briefly, the clinical diagnostic criteria are as follows: (1) history of onset of symptoms at birth or early infancy; (2) varied neurologic symptoms, including convulsions; (3) internal hydrocephalus or microcephaly (the latter being infrequent); (4) focal necrotizing chorioretinitis; (5) roentgenographic evidence of scattered intracranial calcifications; (6) pneumoencephalographic evidence of internal hydrocephalus; (7) mental retardation (not invariably); (8) xanthochromia, pleocytosis of round cell type and high total protein content of the spinal fluid; (9) recovery of toxoplasmas from the blood or cerebrospinal fluid by animal inoculation (mice, rabbits), and (10) demonstration of neutralizing antibodies in the blood of the infant or mother.

Up to the present 11 cases of fatal infantile toxoplasmic encephalitis (Steiner) have been reported, the following case constituting the twelfth.

REPORT OF A CASE

A premature male infant, delivered of a 28 year old primiparous, diabetic mother, became cyanotic two days after birth and had difficult, spasmodic breathing and pronounced jaundice. Fine petechial hemorrhages appeared in the skin. Tremors and twitchings of the fingers and feet were present, and later, during the night, convulsive movements occurred. Examination showed enlargement of the heart, liver and spleen. The clinical picture suggested the presence of erythroblastosis fetalis. On the third day of life the infant suddenly stopped breathing and died.

Necropsy showed icterus, petechial hemorrhages of the skin, splenomegaly, hepatomegaly and undescended testicles. The spleen was three times the normal size, and the liver, which weighed 150 Gm., showed numerous areas of "fatty" degeneration.

The brain, at the time of removal, showed evidence of internal hydrocephalus. The lateral ventricles were moderately dilated. Widely distributed areas of necrosis appeared in both temporal and frontal lobes, the floor of the lateral ventricles and both basal nuclei. Many of the degenerated areas were periventricular.

Histologically, the necrotic lesions which were seen on gross inspection showed all the characteristics of a granuloma plus the deposition of calcareous granules.

The granulomas themselves, with the cell stain, showed three distinct zones: an inner one of necrotic material, a middle zone of granulation tissue and an outer area of tissue reaction. The middle zone was composed of chronic inflammatory elements (lymphocytes, monocytes and plasma cells); fibroblasts; epithelioid cells; large vesicular cells containing debris; occasional polymorphonuclear leukocytes, and a protozoon (Toxoplasma), occurring in cysts, free in the tissue and in phagocytes.

Some of the lesions in the temporal lobe, the cingular gyrus and the hippocampus involved the leptomeninges, and the cellular exudate in the subarachnoid space consisted of chronic inflammatory elements—lymphocytes, plasma cells and monocytes. The toxoplasmas were not present in the subarachnoid space.

The toxoplasmas were seen in and around the granulomas except in the necrotic portions. The appearance of the organisms themselves corresponded in all essentials to that described in the literature. None of the organisms could be seen in ganglion cells. The leptomeninges in the unaffected portion of the brain showed no inflammatory or proliferative reaction.

Our patient was an 8 month premature infant who lived three days. The brain for the most part showed massive granulomatous lesions and no granulomas of the miliary type described by Wolf, Cowen and Paige, Sabin and others. It is evident from the examination of our preparations that the lesions were chronic and antedated the elective cesarean delivery by weeks, if not months. This, obviously, represents a true antenatal type of infection of the brain.

DISCUSSION

Dr. Gabriel Schwarz: I have been interested in toxoplasmosis because there has been an opportunity at the University Hospital to see cases of the arrested disease. Since I reported 2 cases before this society, I have seen 2 others; I have now studied 4 cases of arrested toxoplasmic encephalitis.

Were Dr. Moore and Dr. Winkelman able to culture the toxoplasms by inoculation of mice? Did they send a specimen of serum to Dr. Wolf and his group for neutralization tests? There is certainly needed a more definite test than the neutralization test developed by Sabin. In both cases that I studied at the University Hospital, and in which I sent specimens of serum to Dr. Wolf, some of the control specimens were positive, not so strongly, but certainly positive.

This case reported by Dr. Winkelman and Dr. Moore increases the number of well studied and authenticated cases of toxoplasmosis of the nervous system. I think this condition will be found the cause of more fetal and infantile deaths in the past than has been supposed.

Dr. George Gammon: Was there evidence of kernicterus in this child? Was he jaundiced, with enlarged liver and spleen and erythroblastosis?

Dr. N. W. Winkelman: We did not make any injection experiments on animals because the brain was sent to us after fixation in solution of formaldehyde. The child's mother moved after her discharge from the hospital, and we have no trace of her. In answer to Dr. Gammon's question, the child had the icterus that one sees in many newborn children. It was not icterus neonatorum gravis, and the brain showed none of the changes of the so-called kernicterus.

Dr. Matthew Moore: As Dr. Winkelman stated, the specimen was submitted to us in poor condition, and it was not until histologic studies had been made that the diagnosis became apparent. In order to fulfil all the criteria for the diagnosis of toxoplasmic meningoencephalitis, we should have desired serologic tests on both the infant and the mother; however, this, obviously, was not possible. As was stated in the paper, observers have tested not only the patient and mother for serologic reactions, but other members of the family,

who, surprisingly, have showed a positive reaction for toxoplasmic infection. A representative number of persons from the lay population have had serologic tests for the toxoplasmic infection, and many have given a positive reaction. It is not at all unlikely that toxoplasmic infection in adults is fairly prevalent, but the human adult acquires immunity to the organism and therefore does not manifest clinical signs. In the fetus, however, to which the organism has been transmitted by the mother, there appears to be a susceptibility of the nervous system to the ravages of the organism, and the characteristic meningoencephalomyelitis develops.

AMERICAN ASSOCIATION OF NEUROPATHOLOGISTS

H. M. ZIMMERMAN, M.D., *President, in the Chair*

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Porencephaly. DR. OTTO MARBURG, New York.

A study of the literature on porencephaly reveals two different concepts, one which acknowledges as porencephaly only the condition in which a cavity in the brain connects the ventricle and the subarachnoid space, and the other which considers every simple cavity as constituting porencephaly (incomplete porencephaly, or pseudoporencephaly). The second concept is based on the fact that these simple cavities occur in the same site and present the same pathologic changes as true porencephaly. Surprisingly, the site of the cavities corresponds with the drainage areas of the veins, particularly that of the vena magna Galeni. This fact was proved by the investigations of Siegmund and, in particular, by those of Schwartz. The drainage areas of the respective branches of the veins are well known, as a result of the studies of Schwartz and Fink and Schlesinger. The vena terminalis anterior and the vena lateralis ventriculi are particularly affected, the whole drainage area of the vena magna Galeni being occasionally involved, thus causing cavities within the cerebellum and, via the vena basalis of Rosenthal, at the base of the brain, including the optic chiasm and the optic tract. Involvement of the latter area explains the occasional occurrence of optic nerve atrophy. The intactness of the striopallidum in the majority of the cases under discussion is evidence that there involvement of the arteria cerebri media, as has been suggested by many authors, did not occur. There may, however, be a few isolated cases in which arterial obstruction leads to similar formations.

The cortical foci are cone shaped, as was first demonstrated by Schwartz. Since the veins accompany the arteries, it is obvious that in the frontal area, as well as in the sylvian fissure, the cavities are horizontal, whereas they run dorsoventrally in the region of the central convolutions. The destructive process leading to the formation of the cavity is a necrotic or malacic one, occasionally accompanied by lymphocytes around the blood vessels, due to stasis edema. This, however, is not proof that an inflammatory process is the cause of porencephaly, as was suggested by Strümpell. Concerning this point there is great confusion, since what is called Virchow's encephalitis is in reality malacia following phlebothrombosis or phlebostasis (Wohlwill). This condition is a usual accompaniment of porencephaly. When, however, there is another type of inflammation, either a complicating factor (secondary infection, as in the case of Globus) or phlebothrombosis (as in a case of Ghiberti) causes the destruction. That arrested development is a cause of porencephaly, as was first suggested by Heschl, was disproved by Zingerle, with sufficient evidence. Recently Yakovlev and Wadsworth have tried to bring new evidence in favor of Heschl's suggestion. The course of the clefts, corresponding in their opinion, to zones of cleavage, or primary fissures, depends, as already explained, on the site of the veins. The relation between pia and ependyma is of no significance, since the latter has its own circulatory mechanism, and it is questionable whether the cover of the porus is formed by arachnoid or by newly formed connective tissue. Microgyria is seen in every case of porencephaly, and dystopias are easily explained by the time of onset of the porencephaly. The earlier the onset, the more dystopias will be encountered.

For the formation of porencephaly there must be, in addition, hydrocephalus, with perforation of the thin walls of the cavity. This hydrocephalus is not primary, but is secondary to some lesion of the brain, as d'Abundo and I have proved experimentally.

DISCUSSION

DR. CLEMENS E. BENDA, Wrentham, Mass.: Dr. Marburg has used the term porencephaly for a number of different conditions which should be kept distinct. He uses the term for true porencephaly, which is a congenital malformation developing some time during the second half of the prenatal period, and for the cystic degeneration of the brain which may be the product of birth injury or of infantile encephalitis. These various conditions have different causes, and it is hard to understand an attempt to explain the various operative factors by a single mechanism.

DR. OTTO MARBURG, New York: The term "congenital" does not mean endogenous; even if porencephaly is assumed to be congenital, it still may be due to an exogenous factor, such as trauma to the mother which affects the fetus (Seitz, L.: *Arch. f. Gynäk.* **83**:701, 1907. Jaffé, R. H.: Traumatic Porencephaly, *Arch. Path.* **8**:787 [Nov.] 1929).

Influence of Gonads and Adrenal Glands on the Chemical Composition of the Brain. DR. A. WEIL, New York, and DR. R. A. GROAT, Chicago (by invitation).

It had been shown in previous publications that there is a difference in the phospholipid content of the brain of male and female white rats, which changes during growth and after removal of the gonads. A similar difference was demonstrated between the brain of man and that of woman. The present investigation is concerned with the effect of injections of synthetic estrogen and androgen on the chemical constitution of the brain of the white rat. Testosterone propionate and α-estradiol benzoate were injected into both normal and gonadectomized rats. Injections of homologous "sex hormones" into normal animals did not change the chemical composition of their brains. If, however, the preparation was injected into immature gonadectomized rats, there was a change in the direction of the normal makeup. Heterologous "sex hormones" changed the chemical composition of both normal and gonadectomized rat brains toward the female or the male side respectively. It was more difficult to influence the chemical composition of adult rat brains through the injection of synthetic androgen or estrogen in both normal and gonadectomized rats.

In an attempt to ascertain the influence of other endocrine glands on the brain, changes in the latter organ following ablation of the adrenals were studied.

After removal of the adrenal glands in both male and female white rats, there were an increase in the weight of the brain of more than 10 per cent and a proportional increase of the various chemical constituents, without any qualitative changes. At the same time, the weights of the kidneys, heart, thyroid, testes and prostate were increased proportionally, the hypophysis not being affected.

For more than two hundred years it has been known that congenital aplasias of the cerebral cortex accompanied by atrophy of the hypophysis in man is frequently associated with atrophy of the adrenal glands. Various theories center about primary involvement of either the cerebral cortex or the adrenals. However, the fact that ablation of the adrenals results in enlargement of the brain vitiates the theory which designates the primary role to the adrenals. After hypophysectomy the weight of the adrenal glands is reduced to less than one-fifth their normal weight. Hence it would seem that the atrophy of adrenal glands in cases of hemicephaly or cortical aplasias in man is due to atrophy of the hypophysis, and not of the cerebral cortex.

Acute Fatal Experimental Toxoplasmosis in a Young Monkey. Dr. D. Cowen and Dr. A. Wolf, New York.

The source of human infection with toxoplasmas is probably the large reservoir of toxoplasmosis in rodents and birds. Occasionally, spontaneous infection with this protozoon has been noted in other species. In view of the increasingly frequent recognition of toxoplasmosis in man, it is of interest to note that the disease has not often been observed in other primates.

Spontaneous toxoplasmosis was reported in a monkey (Stentor senilicus) by Thézé, in a baboon (Cynocephalus) by Levaditi and Schoen and in a chimpanzee by Kopciowska and Nicolau. These observations consisted essentially in the chance identification at autopsy of rare and isolated parasites without lesions. The organisms occurred in the brains of 2 animals, and in the bone marrow, spleen and liver, in another. Since 2 of the animals had been inoculated with rodent tissues for other purposes, one is justified in doubting whether the toxoplasmas had not accidentally been introduced.

Since 1909, several attempts have been made to infect primates experimentally by Nicolle, by Levaditi and by Sabin and their various co-workers. Several species of monkeys (Macaca cynomolgus, Macaca sinicus, Macaca rhesus and Cercopithecus patas) and 2 baboons (Papio sphinx) were inoculated with toxoplasmas by various routes, chiefly the intracerebral. For the most part, single representatives of each species were used, and negative results were obtained. It has been shown, however, that adult Macaca rhesus monkeys may manifest clinical and serologic evidence of a mild, transient infection. Pathologic examinations carried out on 3 monkeys and a baboon gave negative results. In brief, a fatal infection in primates has not yet been produced.

In the present experiments, 7 Macaca rhesus monkeys were inoculated by the intracerebral and other routes with human strains of Toxoplasma. Of these animals, 2 were immature, 7 months of age; 2 were young adults; 2 were adult pregnant females, and the last, an infant, inoculated at 2 months of age, was the offspring of one of the 2 females. An adult baboon was also inoculated. One immature monkey, given inoculations of the brain and the peritoneal cavity, had repeated convulsions and died five days after intracerebral inoculation. Autopsy revealed meningoencephalitis, interstitial myocarditis, focal interstitial pneumonitis, focal myositis and small inflammatory lesions in the rete testis. The second immature monkey probably had transient acute toxoplasmosis, from which it recovered. This monkey's serum gave a weakly positive neutralization test for toxoplasmas, but the animal showed no lesions when killed five months later.

All the other animals showed no evidence of toxoplasmosis, either clinically or at autopsy. Of the animals tested serologically, the baboon and 1 monkey gave negative reactions and the 2 pregnant females mildly positive reactions. The attempt to transmit the infection to the fetus by infecting these pregnant monkeys was unsuccessful, but the infant born of 1 of them proved refractory to infection by repeated inoculation. In conclusion, only in 1 immature monkey did a fatal infection develop. This susceptibility of a younger animal is interesting in view of the higher incidence of human toxoplasmosis in the first decade of life.

Histopathology of Cerebral Aneurysms. Dr. F. M. Forster, Wellesley, Mass. (by invitation) and Dr. B. J. Alpers, Philadelphia.

In previous studies on congenital aneurysm a question arose as to the congenital nature of the defect of the media, and the status of the elastica and of the intima was not clearly defined. For this reason, 8 aneurysms of the circle of Willis, all occurring at bifurcations, were studied in serial sections. Hematoxylin and eosin, Van Gieson's stain for elastic tissue and Masson's trichrome stain were employed. All 8 aneurysms arose from an area of defect in the media of the parent vessel. These defects in the media were sharply defined and had not undergone inflammatory or degenerative changes. Study of these defects in serial sections gave evidence that they were not artefacts due to tucking in of the media. In none of the 8 aneurysmal sacs was there any evidence of a medial coat. In contradistinction to this, the condition of the elastic membrane was variable. In 1 specimen it was present and complete in the aneurysmal sac. In 2 specimens the elastic membrane of the aneurysmal wall was entirely lacking, and in 1 of them the elastica of the parent vessel ended abruptly at the point of origin of the aneurysm. In 5 of the aneurysmal sacs elastic tissue was present in varying amounts, but as fragmented strands. In these 5 aneurysms and in 1 of the aneurysms in which the elastica was lacking, the elastic membrane of the parent vessel as it approached the origin of the aneurysmal sac became frayed and split. In 4 of the 8 aneurysmal sacs the intima was normal, and in the remaining 4 sacs it had undergone proliferative and degenerative changes. Changes in the intima and alterations of the elastica were not necessarily coexistent, and either occurred independently of the other.

In view of the constancy of the defect of the media and its freedom from evidence of degeneration or inflammation, it is concluded that the cerebral aneurysm is a true congenital defect. The wide range of alterations of the elastic membrane, from a complete membrane through fragments of elastic tissue to entire absence of such tissue, occurring irrespective of other degenerative changes, indicates a tendency of the elastica to disintegrate in the wall of the congenital aneurysm. In view of the wide range of alterations in the elastica, it is concluded that, regardless of the state of the elastica, such aneurysms should be considered congenital.

DISCUSSION

Dr. Alfred Angrist, Jamaica, N. Y.: The variations in the defects which have been stressed are

enlightening, for heretofore authors have emphasized a defect in one particular coat or another of the vessel, to the exclusion of others. If any one coat of a blood vessel is to obtain undue emphasis, it would seem proper to call attention to the necessity of an intact elastica if aneurysmal bulging, due to increased pressure within the lumen of the vessel, is to be avoided.

It is of interest that the authors noted defects in so-called arteriosclerotic aneurysms. This is in keeping with the observations which my associates and I have made and permits of a unifying concept. It is our impression that many so-called arteriosclerotic aneurysms are basically congenital lesions, and that such congenital lesions have an increased propensity to undergo arteriosclerotic changes of a degenerative nature. It is such changes that lead to the softening and weakening of the sac and to actual rupture and hemorrhage. In all of the congenital aneurysms studied which led to fatal subarachnoid hemorrhage we invariably noted arteriosclerotic changes. It is of interest that occasionally we saw active arteriosclerotic changes with lesions simulating a necrotizing process, or a condition similar to that often observed in the arterioles with malignant nephrosclerosis. Aneurysms which in the gross seemed purely congenital, on microscopic examination showed arteriosclerotic changes, and often acute necrotizing lesions in the wall. According to this concept, the hemorrhage, which is the dramatic complication of these lesions, is explained by the selective localization of the general pathologic process of arteriosclerosis in the aneurysmal sac, while the rest of the vessel usually fails to show such changes. Whether the arteriosclerotic process is brought on by the physical effect of eddies and the stresses in the sac remains a theoretic consideration. The arteriosclerotic process then becomes the basis for the rupture of the congenital aneurysm, much as it is accepted as the basis for ordinary apoplexy.

Giant Cells in Neuroectodermal Tumors of the Brain. Dr. J. H. Globus, New York, and Dr. H. Kuhlenbeck, Philadelphia.

As far back as 1905, the presence of giant cells in gliogenous tumors was described by Babes, and later the observation was confirmed by other authors. In 1918 and 1924 Globus and Strauss studied the type of tumor which they designated as spongioblastoma, and later as spongioblastoma multiforme. Their observations emphasized the role played by giant cells in rapidly growing gliogenous tumors. It was suggested by these authors that the rapidity with which such a tumor grows is related to the presence of these giant cells. From other quarters, however, a theory was advanced that these cells are reactive elements, provoked by necrobiosis. On the other hand, experimental work with tissue culture has in the meantime provided new evidence that the giant cells are a special cell form which can be reproduced in artificial growth mediums.

An attempt to emphasize the importance of giant cells was made by Farnell, in collaboration with Globus, but his preliminary report was based on less abundant material.

Having in the course of the past twenty years collected abundant material from which to choose striking examples of various types of giant cells in various stages of development, we selected 35 neoplasms displaying characteristic varieties of giant cells. These neoplasms belong to seven types of neuroectodermal tumors of the brain: spongioblastoma multiforme, spongioneuroblastoma, spongioblastoma ependymale, transitional glioma, transitional glioneuroma, tuberous sclerosis (spongioneuroblastosis disseminata) and pinealoma.

In this material the formation of giant cells both by true mitotic division and by atypical multipolar mitosis was observed. Tripolar, tetrapolar, pentapolar, and possibly hexapolar, metaphase stages, with the corresponding number of centrosomes, were noted. Other giant cells, however, showed evidence of amitotic nuclear division. Highly irregular amitotic fragmentation and break-up patterns of nuclear material were observed in some instances, while in others the amitotic nuclear, constriction and division figures resembled those seen in normal tissue. On the other hand, phases of explosive mitotic activity leading to rapid tumor growth were noted. True giant cells of spongioblastic, as well as of neuroblastic, lineage were recognized in areas untouched by necrobiotic processes. Multinuclear, as well as mononuclear, giant cells were observed in both spongioblastic and neuroblastic categories. The close relation of such giant cells to the monster cells in tuberous sclerosis (spongioneuroblastosis disseminata) could be demonstrated. Giant cells show not only features of arrested or retarded differentiation, but progressive changes in the direction of further differentiation (Nissl substance, neurofibrillae or astrocytic features).

The sites of predilection of tumors rich in giant cells were the subependymal cell plate, the region of the sulcus terminalis and other sites of embryonic remnants which we have described in previous communications.

In cases of spongioneuroblastoma rounded groups of large neuroblastic cells surrounded by spongioblastic elements could be seen. Individual neuroblastic cells might even appear to be enclosed by small spongioblastic cells, an arrangement imitating that of capsule cells. The entire pattern bore a conspicuous, if only superficial, resemblance to a spinal or a cranial nerve ganglion. Moreover, the giant cells, particularly the mononuclear forms, often bore a strong resemblance to ganglion cells.

The following phylogenetic factor may be invoked to explain this striking tendency to exhibit patterns of structures derived from the neural crest. In Acrania (Branchiostoma; Amphioxus) the primary sensory cells, with few exceptions, remain within the neural tube. The dorsal roots contain no spinal ganglia, and a neural crest is not present. In Petromyzon the neural crest and the spinal ganglia make their first appearance. However, in all fishes large primary sensory cells of the type of spinal ganglion cells are still present in the dorsal portion of the spinal cord. Even in amphibian larvae and reptilian embryos such elements still represent a transitory embryonic feature and are known as the transitory dorsal cells, or Rohon-Beard cells.

It may thus be assumed that the neural crest or the cells of the spinal and the cranial nerve ganglia represent alar elements which were originally enclosed within the neural tube and which secondarily migrated toward the periphery, possibly following a neurobiotactic stimulus, to aggregate as the neural crest and subsequent spinal and cranial ganglia (Kappers, 1920; Kuhlenbeck, 1927).

The nucleus of the mesencephalic root of the trigeminal nerve has thus been interpreted as a group of such primary sensory cells remaining in a phylogenetically primitive position within the neural tube.

As these ganglion-like neoplastic cell groups occur in neuroectodermal tumors within regions derived from the alar plate of the forebrain, it may easily be surmised that they have developed from embryonal cell remnants with primitive ganglionic crest potencies.

DISCUSSION

H. M. ZIMMERMAN (MC), U.S.N.R.: Dr. Globus' contention that the giant cells in malignant gliomas are neoplastic rather than inflammatory is not surprising to the general pathologist. The latter sees giant cells in other types of malignant neoplasms, such as the malignant melanoma, the chorioepithelioma and even certain carcinomas of the stomach. What is surprising is Dr. Globus' statement that the giant cells can and do break up into single nucleated glial tumor cells. It has generally been accepted, I believe, that multinucleated cells were the result of abnormal cellular division, or of cellular fusion, and thus represented a terminal state, or condition, of the cells. That such cells can divide to form single cells is a new idea.

DR. J. H. GLOBUS, New York: I believe the demonstration contains sufficient evidence in favor of cell division, rather than of cell coalescence, as a cause of giant cell formation.

Pathology of Demyelinating Diseases as an Allergic Reaction of the Brain. DR. A. FERRARO, New York.

This paper was published in the December 1944 issue of the ARCHIVES, page 443.

Periarteritis Nodosa with Decerebrate Rigidity and Extensive Encephalomalacia in a Five Year Old Child. DR. N. MALAMUD, Ann Arbor, Mich.

The occurrence of periarteritis nodosa in childhood is not uncommon. But although there is considerable clinical evidence of involvement of the central nervous system in children with this disorder, there are few clinicopathologic reports in the literature, and, for this reason, the following case is presented.

REPORT OF A CASE

A 5 year old boy, while convalescing from an infection of the upper respiratory tract, had fleeting joint and abdominal pains. Examination revealed a systolic cardiac murmur, fever and leukocytosis, which led to a diagnosis of acute rheumatic fever. A week later, just as these symptoms began to subside, the patient suddenly had a series of convulsive seizures, became comatose and presented outspoken signs of complete decerebrate rigidity. The pupils were dilated and fixed to light, and there was mild papilledema. The temperature became elevated and irregular. Ventriculographic studies suggested a tumor of the brain stem. The patient's condition declined rapidly, and he died approximately two and a half months after the onset of the illness.

Necropsy revealed massive necrosis of the cerebrum. The entire cortex and the basal ganglia were spongy and friable, resembling milk curds, and were poorly demarcated from the somewhat firmer white matter. In Nissl preparations the necrotizing process could be traced down to the level of the red nucleus, where it stopped abruptly. Histologically there was noninflammatory, complete liquefaction necrosis of the tissue in a uniform stage of active gliomesodermal reaction. The brain stem and the spinal cord were intact, and there was only diffuse degeneration of Purkinje cells in the cerebellum. All the basal vessels were normal, but careful microscopic examination of the vessels in large sections revealed typical changes of periarteritis nodosa in the smaller meningeal arteries on the medial surfaces of the cerebral hemispheres. The disease was in a subacute phase, consisting in "hyaline" necrosis of the subintima and media, perivascular infiltration with lymphocytes and beginning fibrosis of the intima and adventitia, with narrowing of the lumen. Similar vascular lesions were present in the heart, resulting in anemic infarcts throughout the myocardium and a solitary aneurysm of the left marginal branch of the coronary artery. There were some lesions in the wall of the trachea, the gastrointestinal tract and the kidneys.

This case was unique in many ways. The clinical course was unusual in that only the brief initial symptoms were suggestive of periarteritis nodosa. These early signs were quickly obscured by a purely neurologic syndrome of decerebrate rigidity, so that a diagnosis of cerebral tumor was considered. There was a striking disproportion between the extensive destruction of the cerebral parenchyma and the restricted vascular lesions. This discrepancy has been observed by other authors, but probably only the case described by Baló was one of comparable severity. While periarteritis nodosa is admittedly a vascular disorder, this lack of parallelism between the vascular and the parenchymal involvement in some cases must be accounted for by other factors. Some authors attribute this to a toxic factor. In my opinion, the view recently substantiated experimentally by Rich and Gregory that periarteritis nodosa is an anaphylactic type of reaction is of interest in this connection. In the present case, the onset of the disease after an infection of the upper respiratory tract and its initial general effect on various tissues of the body, followed suddenly by an extensive necrotizing process in the brain, out of all proportion to the arteritis, suggest an allergic reaction.

DISCUSSION

DR. A. FERRARO, New York: The material presented by Dr. Malamud is of interest because it is in accord with the new concept of an allergic reaction of the brain in the presence of certain pathologic conditions. It is gratifying that he, too, has been thinking in such terms. Among such pathologic changes of particular interest is the periarteritis nodosa which he has described, and it is well known that such a condition is now considered the expression of an allergic reaction of the blood vessel walls. In view of this interpretation of the vascular damage, I agree with him that the rest of the pathologic picture can be viewed in the light of a more general allergic reaction of the brain tissue. I feel confident that the study of allergic reactions of the brain to various pathologic stimuli will open a bright new field for investigation and better understanding of brain pathology.

Cerebral Thromboangiitis Obliterans: Histogenesis of Early Lesions. DR. I. MARK SCHEINKER, Cincinnati.

This paper was published in full in the July 1944 issue of the ARCHIVES (**52**:27, 1944).

Neurogenic Polycythemia: Report of a Case. DR. A. EARL WALKER, Chicago.

Neurologic phenomena accompanying polycythemia vera are usually considered the result of the polycythemia, but a growing volume of literature has been accumulating suggesting that the cerebral lesions may be the primary factors in the production of the erythremia. Within the past four years I have performed operation in 2 cases of cerebellar hemangioblastoma associated with polycythemia, which disappeared after

removal of the tumor, and Dr. Henry Schwartz operated in a similar case. Two of these cases have previously been reported (Carpenter, G.; Schwartz, H., and Walker, A. E.: Neurogenic Polycythemia, *Ann. Int. Med.* **19**:470-481, 1943). A brief summary of the third case follows.

A. G. F., a machine operator aged 32, was admitted to the University of Chicago Clinics on Sept. 3, 1943, complaining of throbbing headaches of five months' duration. Except for erythematous papules on the face, physical examination gave normal results. Neurologic examination revealed only unsteadiness of gait. Examination of the blood showed a high erythrocyte count and elevation of hemoglobin but a normal white cell count, indicating that the erythrocytosis was not the result of dehydration. Spinal puncture revealed increased intracranial pressure (300 mm. of cerebrospinal fluid). Since ventriculographic study showed no dilatation of the cerebral ventricular system the patient was treated with phlebotomy, 1,000 cc. of blood being removed on two occasions. His condition, however, did not improve, although the degree of erythrocytosis decreased. On November 25 he was found to have papilledema; a second ventriculographic examination revealed symmetric internal hydrocephalus with anterior displacement of the aqueduct of Sylvius.

On November 30 the posterior fossa was exposed and a vascular tumor removed from the posterior part of the left hemisphere. The patient had an uneventful convalescence and was discharged to his home on the eighth postoperative day. Histologic study revealed that the neoplasm was a hemangioblastoma.

The plasma volume did not appreciably change after operation, although the red cell mass decreased almost 1 liter. This finding suggests that the condition was a real polycythemia, and not merely a hemoconcentration. It is true that the erythremia was never severe, but in view of the patient's weight the hematologic picture appears abnormal.

The presence of erythrocyte-regulatory centers in the diencephalon has been suggested by Schulhof and Mathies, da Rin and Costa, and Riccitelli, on experimental grounds. The clinical basis for such a hypothesis has recently been reviewed by Ferraro and Sherwood (*Psychiatric Quart.* **11**:19, 1937).

Apposite to this discussion is mention of the well controlled work of Schafer in production of erythremia, with a red cell count as high as 9,000,000 per cubic millimeter, in dogs by section of all afferent depressor fibers in the cervical region. The great increase in blood volume accompanying the polycythemia was shown to be due entirely to increase in the cell volume. Total sympathectomy abolished or prevented this effect. Hypertension with vasoconstriction is an essential part of the syndrome produced by section of the depressor fibers, and it is possible that the operation is nothing more than a surgical method of producing the type of polycythemia which Davis induced in man and animals with vasoconstrictor drugs. On the other hand, its implications with respect to possible erythrocyte-controlling centers cannot now be discounted.

In no instance of "neurogenic polycythemia" has there been described any notable enlargement of the spleen. This perhaps is in keeping with the concept of the erythremia as essentially symptomatic, it being widely held (though unproved) that splenic enlargement is due to the storage of cells unwanted by the circulation.

That the pathologic type of the tumor may have played an etiologic role in the polycythemia is not probable in view of the fact that in none of a series of 14 other cases of cerebellar hemangioblastoma was there any evidence of erythremia. Nor did Cushing and Bailey mention such a complicating condition in their review of the subject.

It is unlikely that an arteriovenous shunt in the cerebellum through the vascular tumor could be the cause of the polycythemia. Unfortunately, however, determinations of oxygen tension of venous and arterial blood for the head were not made, so that such a possibility cannot be entirely eliminated.

It may only be said at this time that polycythemia associated with cerebellar hemangioblastoma has been observed in 3 cases. The pathogenesis of the polycythemia must remain for further clinical and experimental studies to determine.

DISCUSSION

DR. L. ROIZIN, New York: Could the polycythemia noted in Dr. Walker's 2 cases be related to a neurohormonal mechanism? I ask this for the following reason:

In 1935, in collaboration with Dr. P. Foa (*Arch. di fisiol.* **35**:170, 1935), I investigated the influence of the central nervous system on the morphologic composition of the blood in dogs. In our experiments we studied the effects of the hydrodynamic changes in the spinal fluid pressure, the action of various vegetative-mimetic drugs and glandular preparations introduced into the cerebral ventricles and the influence of generalized convulsions produced by strychnine applied to the cortical motor region, followed by cutaneous stimulation of the area. Simultaneous registration of the blood pressure and oncographic study of the spleen and bone marrow (Tournade's method) revealed that increase in blood pressure and decrease in volume of the spleen were associated with erythrocytosis and leukocytosis (neutrophilia, lymphopenia and a shift to the left of Arneth's formula). In splenectomized dogs less pronounced erythrocytosis and slight leukopenia were noted. Variations in number of the white and the red blood cells also were observed in relation to emotional states in the animals. We concluded that the temporary increase of the white and the red blood cells was related to the stimulation of the neurovegetative centers of the diencephalon and medulla. Somewhat similar results were noted also by Borchardt in adrenalectomized cats and by Anderson and Witthower in human beings.

I wonder whether the polycythemia observed in Dr. Walker's cases before the operation and the return to normal afterward could be related to similar neurohormonal mechanisms elicited by abnormal pressure of the tumor or by hydrodynamic variations in the cerebrospinal fluid.

DR. H. M. ZIMMERMAN (MC), U.S.N.R.: Was there any evidence of hematopoiesis in the case of cerebellar hemangioblastoma?

DR. A. EARL WALKER, Chicago: The observations to which Dr. Roisin referred were disturbances of the entire hematopoietic system, which were not present in our cases of polycythemia associated with cerebellar hemangioblastoma. The erythremia in our cases was related to the red cell–forming mechanisms alone and probably is to be explained by a peripheral disturbance induced by the neuropathologic process. That intracranial hypertension alone produces polycythemia is not likely, since we were unable to find evidence of such a condition with other types of cerebral tumor associated with intracranial hypertension. The precise mechanism of the disorder must be left for further investigation.

Dr. Zimmerman asks whether there was any evidence of hematopoiesis. In these cases of symptomatic polycythemia, as is true in practically all such cases, there was no increase in the nucleated red cells. Unfortunately, biopsy of the bone marrow was not made in any of our cases, so that more direct evidence of increased hematopoiesis is not available.

Coagulation Necrosis in the Brain. DR. KARL T. NEUBUERGER, Denver.

This condition is more frequent than one would conclude from the literature. The anatomic picture exhibits the following main characteristics: more or less complete necrosis of the tissue; presence of doubly refractive, acicular "slits" (apparently the site of cholesterol crystals) and sometimes of amyloid bodies and extracellular lipid droplets; varying degrees of calcification (granules or fibrils), and absence of decomposition and organization inside the necrosis. The foci are sometimes present within softened tissue; they may become surrounded and replaced with collagen tissue, with islands of foam cells. Grossly, the foci are small, whitish and moderately firm.

The recent literature contains only a few related papers (Markiewicz; Ley; Credé). The material used in this study consisted of 18 cases, in which arteriosclerosis, trauma, neoplasm, embolism and meningitis were represented (slides).

The difference between this type of necrosis and liquefaction necrosis is evident. During only the earliest stages of an infarct in the brain is one unable to state in which direction the development will proceed. Coagulation necrosis differs also from caseation: An area of caseation is surrounded by specific granulation tissue; it is characterized by deposition of fibrinoid masses, preservation of elastic tissue and absence of slits. Coagulation necrosis in the brain has been compared to infarcts in the viscera (kidney and spleen). While such a comparison is partially justified, especially with regard to pathogenesis, it is not completely satisfactory. The fact that brain tissue undergoing necrosis is chemically different from visceral tissue should be considered. The brain is rich in cholesterol. Disintegration of the brain tissue, due to failing nutrition, sets free cholesterol esters; these substances are split, and cholesterol crystallizes, with formation of "slits." This process may be compared with what happens, for example, in atheromatous softening of the aorta. The breakdown may take place in areas of simple necrosis of brain tissue, or it may occur in tissue revivified by gitter cells.

The lesion is due apparently to complete ischemia of the region involved. In the cases examined, so far as could be determined, there was total or subtotal vascular occlusion. It is perhaps superfluous to bring in the term "fermental preparation" (*Aufbereitung*), as used by Markiewicz. He expressed the belief that such a preparation takes place in areas of ordinary softening under the influence of surrounding living tissue, which furnishes the ferments required; this preparation is said to be missing with coagulation necrosis. However, in softening of circulatory origin revivification arises not only from the surrounding tissue but from mesenchymal and glial tissues within the focus; one may assume that the nutritional supply is sufficient to maintain the reactability of the supporting tissue. It has been observed often that the center of a large infarct fails to become revivified and undergoes coagulation necrosis while the periphery displays the usual softening; in such cases there probably was an incomplete nutritional supply to the periphery, with total absence of such supply to the center. That a focus with early features of softening breaks down later and undergoes coagulation necrosis is due most likely to eventual deterioration of the nutritional supply.

DISCUSSION

DR. F. WERTHAM, Jamaica, N. Y.: Were the lesions of coagulation necrosis which Dr. Neubuerger described acute, or does he know of prestages out of which they developed?

DR. KARL T. NEUBUERGER, Denver: The lesions were either primary, with subacute to chronic development, or, in some instances, secondary, arising from preceding early stages of customary softening; this is indicated by the presence of occasional groups of gitter cells within the foci.

Lipoma in the Quadrigeminal Plate with Hydrocephalus: Report of a Case. DR. CHARLES DAVISON.

Lipoma of the central nervous system occurs chiefly in the region of the cisternal enlargements of the subarachnoid space and is closely attached to the meninges, the vessels or the nerves traversing the meninges. To date, about 80 cases of lipoma of the central nervous system have been reported. The superior surface of the corpus callosum and the tuber cinereum are the most common sites. In 8 cases of lipoma, including the present case, the site was the region of the quadrigeminal plate and around the trochlear nerve. In none of these cases, except Taubner's and mine, were symptoms noted. This neoplasm, which originates in the leptomeninges, a derivative of the neural crest, may grow along the nerves and vessels into the brain or the cord tissue and simulate infiltrative growths or give the impression that it actually arises from the neural elements. Frequently it compresses and distorts the nerve tissue. Most observers believe that the lipoblast which gives rise to the lipoma in the central nervous system originates from the mesenchyme, which, in turn, is a derivative of the ectoderm or the endoderm, arising apparently at the junction of these two germinal layers.

REPORT OF A CASE

A man aged 53, gainfully employed, had been born with a large head. A hopeless prognosis was made at birth. He did not attend school but was tutored up to the age of 14 years.

Examination disclosed symmetric enlargement of the calvaria, which measured 75 cm. in circumference. The left pupil was slightly larger than the right. Ocular movements were normal except for defect in convergence of the left eye. Air and bone conduction were diminished in the right ear. There was slight hyperreflexia in the left lower extremity. He was euphoric. Intelligence was about average. Toward the end of life, his ability to remember faces and names was poor.

At times he became noisy and complained of severe frontal headaches. During the last month there developed a subnormal temperature, which on several occasions dropped to 94 or 95 F. It persisted for one month, until his death.

Autopsy.—The lipoma extended from the inferior border of the superior colliculi to almost the lower limit of the fourth ventricle. The entire fourth nerve had disappeared except for a few partially demyelinated fibers, some of which were embedded in the tumor. The aqueduct of Sylvius was constricted, distorted and displaced practically throughout its length. There was

severe generalized hydrocephalus. The tumor was a typical lipoma.

DISCUSSION

H. M. ZIMMERMAN (MC), U.S.N.R.: I have observed 3 cases of intracranial lipoma in my necropsy material. In 2 cases the lipoma, which was asymptomatic, was situated in the quadrigeminal plate and was not associated with hydrocephalus. Dr. Harvey Cushing mentioned the first of these cases in his book on meningiomas. The third case was that of a lipoma in the region of the mamillary bodies. The tumor not only destroyed these structures but involved the mamillothalamic tracts. The patient had long-standing hyperthermia, of several years. The clinical and anatomic observations in this case were reported in the symposium on the Hypothalamus (*A. Research Nerv. & Ment. Dis., Proc.* [1939] **20**:824, 1940).

DR. F. WERTHAM, Jamaica, N. Y.: Were there lipomas of the skin in Dr. Davison's case? It is my impression that this lipoma is multiple, but from the data in reported cases I cannot draw a definite conclusion.

DR. CHARLES DAVISON: In my case there were no lipomas of the skin. In some cases multiple lipomas were present in the central nervous system and in other parts of the body.

Encephalitis Affecting the Basal Ganglia in Monkeys. DR. RICHARD RICHTER, Chicago.

The observations presented concern the pathologic observations on 2 monkeys (Macaca mulatta) with acute encephalitis of unknown cause. One of the animals had been inoculated two months before with suspensions of brain tissue from a patient who had died of chronic encephalitis, and the other had been subjected four months previously to bilateral temporal lobectomy. It was concluded, nevertheless, because of the long latent intervals between the experimental procedure and the onset of the acute cerebral disease, as well as for other reasons, that the terminal encephalitis was not due to the experimental factor, but was spontaneous in origin.

The principal lesions, which were of a necrotizing inflammatory type, were similar in the 2 animals and were strictly confined to the corpus striatum and the globus pallidus, but chiefly to the striatum. They were represented by bilateral focal, round areas of necrosis, sometimes confluent, which appeared, even grossly, as areas of "paling." In them no ganglion cells remained, but only a pale, structureless ground substance, within which were degenerated pyknotic glial nuclei and remnants of thickened, swollen blood vessels. In none of the lesions were there any fat granule cells or other evidence of release of fat; the lesions were not softenings but were foci or coagulation necrosis. At the borders of many of these lesions there were proliferation and hyperplasia of the neuroglia and perivascular and interstitial infiltrations of mesodermal inflammatory elements, in which polymorphonuclear leukocytes were prominent. Scattered, diffuse inflammatory changes of the microglia, with rod cell formation, were also observed at a distance from the necrobiotic areas in the caudate nucleus, the lenticular nucleus and the thalamus. In 1 of the animals foci of encephalitis, chiefly microglial, were present in the cerebral and cerebellar cortex; and in both monkeys there were inflammatory infiltrations of the meninges, slight in 1 animal but intense in the other. However, no destructive foci appeared in the cortex or elsewhere, except in the basal ganglia.

Occurrence of lesions of this type, with this localization, has not hitherto been reported in the monkey. Indeed, there are surprisingly few descriptions of spontaneous disease of the nervous system in primates. The reports that exist were reviewed briefly and the observations compared with the material present.

It is noteworthy that in 1 of these animals there developed rapid and extremely violent choreic movements which involved the trunk and the extremities, persisted for two days and then rapidly diminished. These were combined with severe ataxia, resembling that seen in Sydenham's chorea. Perhaps the greatest interest of this material attaches to the association of the chorea and destruction restricted to the basal ganglia, particularly to the corpus striatum. This, of course, corresponds to the accepted and frequently observed association of striatal damage with human chorea, but hitherto such a correlation has not been clearly observed in animals. Attempts to reproduce amyostatic syndromes in primates and other animals by ablation of or injury to the corpus striatum have been singularly fruitless, and there has been general agreement among almost all investigators since Kinnier Wilson that lesions confined to the striatum, even when large, fail to evoke noteworthy symptoms. Recently Fulton and Kennard, after inflicting unilateral and bilateral damage on the striatum of many primates, concluded that such lesions had no visible effect on motor performance when the nervous system was otherwise intact. They did, however, succeed in producing chorea in chimpanzees and monkeys in which ablation of cortical areas 4 or 6 were combined with bilateral destruction of the striatum. The results of ablation experiments are thus corroborated and extended by these observations on spontaneous striatal disease in monkeys. The material demonstrates, in addition, that chorea may appear in the monkey in the presence of basal ganglion disease alone, with an otherwise intact nervous system.

DISCUSSION

DR. A. WEIL, Chicago: Bilaterally symmetric necrosis of the corpus striatum of a monkey, similar to that which Dr. Richter demonstrated in his lantern slides, were produced by Crandall and Weil in a dog by ligation of the common bile ducts (Pathology of the Central Nervous System in Disease of the Liver, ARCH. NEUROL. & PSYCHIAT. **29**:1066 [May] 1933).

Were there any functional or histopathologic changes in the liver in this monkey?

DR. F. WERTHAM, Jamaica, N. Y.: I should like to ask Dr. Richter about the relation of the condition in his animals to the spontaneous diseases in monkeys described by Bodechtel and Scherer.

DR. RICHARD RICHTER, Chicago: In answer to Dr. Wertham's question, Bodechtel described a spontaneous disease in a monkey which was characterized by mild meningeal infiltrations, retrogressive changes in the ganglion cells and pronounced perivascular infiltration of lymphocytes and plasma cells, together with the glial reaction, which consisted especially in proliferation of rod cells. While these changes were qualitatively similar in some respects to the lesions in my monkeys, the localization was quite different, since it was chiefly in the cortex and there was a little inflammatory reaction in the basal ganglia or elsewhere in the nervous system. A somewhat similar inflammatory condition appearing spontaneously in a larger group of monkeys was reported by van Bogaert and Scherer, in which necrobiotic changes, combined with an intense glial and mesodermal inflammatory reaction, were present in the cerebral cortex, particularly that of the occipital lobes. This group of monkeys exhibited blindness, ataxia and convulsions, and in none of them was there any involve-

ment of the basal ganglia. In another report Scherer described disseminated demyelinating lesions deep in the cerebral hemispheres and in the white matter of the spinal cord of monkeys which became ill in epidemic fashions. The disease in these animals had nothing in common with the condition which I have described.

In answer to Dr. Weil's question, the liver of the first monkey presented no noteworthy changes on microscopic examination. There was no opportunity to study the liver of the second animal.

Histologic Changes in a Case of Paramyoclonus Multiplex. Dr. George B. Hassin, Chicago, and Dr. Richard Kepner, Honolulu, Hawaii (by invitation).

Pathologic observations in cases of motor restlessness, described in 1881 by Friedreich as paramyoclonus multiplex, are rare, while the cause and localization of the lightning-like muscular contractions, usually devoid of synchronism and symmetry, are on the whole not known. They have been looked for in vain in the central and peripheral nervous systems and in the muscles themselves. More successful were studies on the type of paramyoclonus which is associated with epilepsy—the so-called epileptic myoclonia, or myoclonus epilepsy. In cases of this form, cerebral changes have been demonstrated in the nerve cells in the form of cytoplasmic inclusions, so well described recently by Ferraro and Roisin (*J. Neuropath. & Exper. Neurol.* **1**:297, 1942). Unfortunately, the muscles were not studied by these investigators.

A generous supply of muscle tissue was obtained for biopsy from an elderly psychotic woman who for years had been an inmate of the Territorial Hospital in Honolulu. For about ten years she had exhibited involuntary contractions in various muscles of the upper and lower extremities and the neck. The contractions would disappear for two or three months and then recur with the same vigor. The specimens of muscle, which were stained with hematoxylin and eosin and by Van Gieson's method, exhibited for the most part normal muscle fibers, of normal size and possessing normal striations. In some muscles the Cohnheim fields were disrupted, and vacuoles were present, while the sarcolemma, the endomysium and the walls of the blood vessels showed nuclear hyperplasia. In general, the parenchymatous changes, though present, were mild and were much less in evidence than the mesodermal changes. Neither type of lesion, however, was commensurate with the severity of the clinical manifestations and differed greatly from the lesions seen in cases of Landry's paralysis, amyotonia congenita and progressive muscular dystrophy. They were probably secondary to, or the result of, muscular hyperactivity of many years' duration. Muscular hyperactivity may result, for instance, in hypertrophy of the muscle fibers, as was stated by Ramsay Hunt in 1903. In a subsequent contribution, however, he expressed the opinion that the hypertrophy was the result of hyperactivity, that is, was secondary. The causative process of paramyoclonus multiplex is thus most likely a lesion in the central nervous system, such as produces the epileptic myoclonia of Unverricht and Lundborg. The Friedreich and the Unverricht-Lundborg type are evidently one disease process, a peculiar form of epilepsy, of which the Friedreich type is the incomplete form. Electroencephalographic and other studies would be of great interest in the investigation of these two forms of paramyoclonus multiplex, as well as of a third form, classified as hysterical.

Book Reviews

Symptoms of Visceral Disease: A Study of the Vegetative Nervous System in Its Relationship to Clinical Medicine. By Francis Marion Pottenger, A.M., M.D., LL.D., F.A.C.P. Sixth edition. Cloth. Price, $5. Pp. 442, with 87 illustrations in text and 10 color plates. St. Louis: C. V. Mosby Company, 1944.

The subtitle of Pottenger's book is its best description. It is concerned with psychosomatic medicine in the strict sense. The author's background—he is a specialist in diseases of the chest—led him to the subject in an attempt to discover why one disease causes different symptoms in different patients. He finds much of the answer in analysis of the many factors involved in production of symptoms. These factors include a multiplicity of visceral reflexes with individual thresholds, relative sympathicotonia and parasympathicotonia, ionic intracellular differences and hypersensitivity phenomena. The principal emphasis is placed on the vegetative nervous system, which determines the division of the book into four parts: the introduction; the vegetative nervous system; its relationship to symptoms of visceral disease; and the innervation of important viscera, with the study of viscerogenic reflexes.

Pottenger's point of view is unitarian: His orientation is to the patient rather than to the disease. That he has succeeded in his chief goals is attested by the fact that the present edition is the sixth; on the other hand, one wishes that he might have incorporated more new material.

The content, which is factual and detailed, does not allow for easy reading. For subsequent editions one would suggest summaries at chapter ends wherever possible. There is a dearth of newer references in the anatomic and physiologic sections, with few, if any, later than 1937; the great majority are far earlier.

The book is of unquestionable value to the internist, as well as to the neurologist and the psychiatrist. It covers a field too often neglected by persons who should be most familiar with it. The book is highly recommended.

An Introduction to Physical Methods of Treatment in Psychiatry. By William Sargant and Eliot Slater. Price, 8s, 6d. Pp. 171. Edinburgh: E. and S. Livingstone, Ltd., 1944.

This book, according to the authors, was written primarily for the student, the young psychiatric clinician, the general practitioner and the psychiatric nurse. The central aim is to present certain of the physical therapeutic methods used in psychiatry with regard to indications, technics, advantages, disadvantages and results. Under discussion are the various insulin technics, metrazol and electric convulsion therapy, the drugs used in treatment of epilepsy, the various sedative and stimulant drugs, the role of diet, vitamins and endocrine preparations, the malarial treatment of dementia paralytica, and, finally, prefrontal leukotomy. All this material is handled objectively, and, while the tone in general is perhaps slightly optimistic, no glowing claims are made for any one procedure.

The chief discussion and criticism of the book will probably come in relation to the emphasis on the so-called constitutional approach. This is expounded in the "Introduction," which is preceded by the following quotation from Henry Maudsley, dated 1870. "The observation and classification of mental disorders have been so exclusively psychological that we have not sincerely realized the fact that they illustrate the same pathological principles as other diseases, are produced in the same way, and must be investigated in the same spirit of positive research. Until this be done, I see no hope of improvement in our knowledge of them, and no use in multiplying books about them."

While the authors in general ascribe to the concept of multicauses, the psychosomatic approach, treatment of the patient as a whole, etc., they lay great emphasis on the so-called genetic potentiality, with the omnipotent genes exerting their specific effects at different developmental periods. Thus, "Inherited tendencies to dementia praecox, involutional melancholia, and to senile dementia lie hidden through the years to manifest themselves in due course when the appropriate time comes." Similar tendencies to anxiety, worry, obsessional thinking and hysterical phenomena are described.

The authors, further, are of the school that believes that everything can, and eventually must, be explained in physiologic terms. Psychologic differences are, therefore, finally to be explained in terms of altered physiologic function.

The book would seem to be of value in relation to its objective presentation, in a brief volume, of a set of physical therapeutic methods in psychiatry. Its theoretic aspects are dogmatically stated with a goal of simplicity, and at the usual cost.

Spina Bifida and Cranium Bifidum. By Franc Ingraham. Pp. 216, with illustrations. Cambridge, Mass.: Harvard University Press, 1944.

This is a bound collection of five reprints which appeared in the *New England Journal of Medicine*. It gives an account of the numerous cases of meningocele, spina bifida and allied conditions which have been observed at the Children's Hospital over many years, analyzed in modern terms. The author's operative methods, indications and results are presented.

Particularly interesting is the description of a series of 20 cases of the Arnold-Chiari malformation. The author recommends operation in cases in which the general neurologic condition is good, though he is not optimistic as to the results.

All in all, the papers present a creditable report on a long term investigation, which is still in progress.